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(54) Title: INHIBITION OF 5-LIPOXYGENASE AND CYCLOOXYGENASE PATHWAY MEDIATED DISEASES

(57) Abstract

A method of dual inhibition of 5-lipoxygenase pathway mediated diseases and cyclooxygenase pathway mediated diseases in a subject in need thereof which comprises administering to such subject an effective, non-toxic 5-lipoxygenase pathway inhibiting amount or an effective, non-toxic cyclooxygenase pathway inhibiting amount of a diaryl-substituted imidazole fused to a second unsaturated 5 or 6 membered heterocyclic ring containing a nitrogen bridgehead atom wherein said second 5 membered ring also contains a sulfur or oxygen atom or said 6 membered ring may also contain an additional nitrogen atom.

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INHIBITION OF 5-LIPOXYGENASE AND CYCLOOXYGENASE PATHWAY MEDIATED DISEASES

FIELD OF THE INVENTION

This invention relates to a method of treating 5-lipoxygenase and cyclooxygenase pathway mediated diseases.

BACKGROUND OF THE INVENTION

The metabolism of arachidonic acid occurs by many pathways. One route of metabolism is via the cyclooxygenase (CO) mediated pathway which produces PGH_2 which is in turn metabolized to the prostanoids (PGE_2, TxA_2, and prostacyclin). These products are produced by various cells including polymorphonuclear leukocytes, mast cells and monocytes. Another route is by the lipoxygenase mediated pathway which oxidizes arachidonic acid initially to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) which is further metabolized to LTA_4, the precursor to the peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) and LTB_4. Additionally 5-HPETE is converted to 5-hydroxyeicosatetraenoic acid (5-HETE).

Lipoxygenases are classified according to the position in the arachidonic acid which is oxygenated. Platelets metabolize arachidonic acid to 12-HETE, while polymorphonuclear leukocytes (PMNs) contain 5 and 15 lipoxygenases. It is known that 12-HETE and 5,12-diHETE are chemotactic for human neutrophils and eosinophils, and may augment the inflammation process. 5-HPETE is known to be a precursor to the peptidylleukotrienes, formerly known as slow reacting substance of anaphylaxis (SRS-A) and LTB_4. The SRS family of molecules, such as leukotrienes C_4 and D_4 have been

shown to be potent bronchoconstrictors. LTB4 has been shown to be a potent chemotatic for PMNs. The products of the 5-lipoxygenase pathway are believed to play an important role in initiating and maintaining the inflammatory response of asthma, allergy, arthritis, psoriasis, and inflammatory bowel disease. It is believed that blockage of this enzyme will interrupt the various pathways involved in these disease states and as such inhibitors should be useful in treating a variety of inflammatory diseases, such as those inumerated above. The absence of selective inhibitors of lipoxygenase, as opposed to cyclooxygenase, which are active in vivo has prevented adequate investigation of the role of leukotrienes in inflammation.

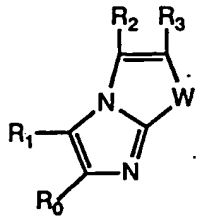
The arachidonic acid oxygenated products, as noted above, have been identified as mediators of various inflammatory conditions. The various inflam-matory disease states caused by these mediators and many other conditions, as discussed herein, are all conditions in which an oxygenated polyunsaturated fatty acid metabolite inhibitor, such as a 5-lipoxygense (5-LO) inhibitor, would be indicated.

The arachidonic acid oxygenated products, as noted above, have been identified as mediators of various inflammatory conditions. Such inflammatory conditions are rheumatoid arthritis, bronchial inflammation, inflammatory bowel disease, asthma, cardiovasular disorders, glaucoma, emphysema, acute respiratory distress syndrome, lupus, gout, psoriasis, pyresis, pain and other allergic oriented disorders such as allergic rhinits, food allergies, and uticaria. These disease states and additional condiditions such as blood platelet aggregation, and notably conditions resulting from thrombosis, including total or partial thrombosis, coronary thrombosis, phlebitis and phlebothrombosis (also associated with inflammation), are all conditions in which a dual inhibitor of both CO and 5-LO would be indicated.

There remains a need for treatment, in this field, for compounds which are effective inhibitors of the products formed by oxygenation of poly-unsaturated fatty acids, such as arachidonic acid. By inhibition of the oxygenated polyunsaturated fatty acids (hereinafter OPUFA), such as by inhibiting the enzymes 5-lipoxygenase (5-LO) and cyclooxgenase (CO) the formation of various leukotrienes and prostaglandins will be prevented.

SUMMARY OF THE INVENTION

This invention relates to a method of treating an OPUFA mediated disease in a subject in need thereof which comprises administering to such subject an effective OPUFA inhibiting amount of a compound of the formula



FORMULA (I)

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3} alkan-amido), N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, C_{1-3} alkylamino, N-(C_{1-3}alkyl)-N-(C_{1-3} alkanamido, C_{1-3} dialkylamino, amino, N-pyrrolidino or N-piperidino;

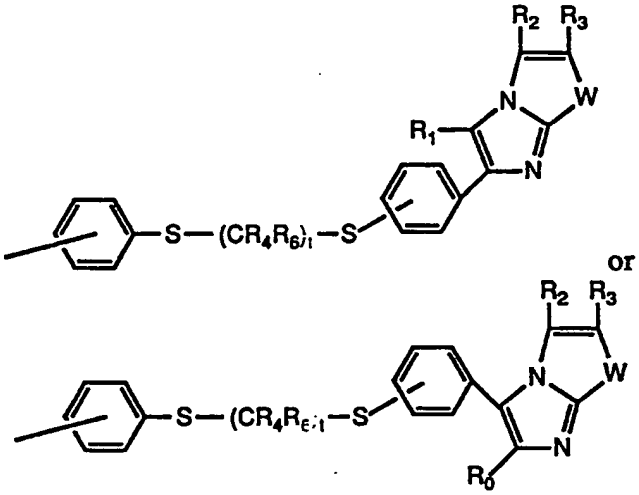
(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl or CF_3, and the other substituent is thiol, alkylsulfinyl, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(d) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl,

alkoxyalkylthio, alkoxyalkyls lfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(e) disubstituted phenyl v ierein said substituents are the same and are selected from halo, C_{1-3} alkc y, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2, 2-trihaloethoxy, prop-2-ene-1-oxy, hydroxy, C_{1-3} alkylthio, C_{1- alkylsulfinyl, C_{1-3} alkyl-sulfonyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} -1-alker l-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, thiol, acyl io, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkyl io, carbalkoxy-alkylthio, alkoxycarbonyl-thio, alkoxythionothio, phen hio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthi lkylthio, Z, or acyloxyalkylthio; or wherein the substituents together form methylene dioxy group;

(f) a moiety of one of the llowing formulae:



or

wherein t is 0 or 1;

R_4 and R_6 are independently elected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;

Z is $-S-(CR_4R_6)_t-S-Z_1$;

Z_1 is C_{1-9} alkyl, aryl or hete aryl;

or a pharmaceutically acceptable salt thereof

Another aspect of this inventior elates to a method of treating a cyclooxygenase pathway mediated disease i a subject in need thereof which comprises administering to such subject an effective, n n-toxic cyclooxygenase pathway inhibiting amount of a compound of Formula (I).

Another aspect of this invention relates to the novel compounds of Formula (II) and a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and an effective amount of a compound of Formula (II).

Another aspect of this invention relates to a method of treating an OPUFA mediated disease in a subject in need thereof which comprises administering to such subject an effective, OPUFA inhibiting amount of a compound of Formula (II). The compounds of Formula (II) are also effective cyclooxygenase inhibitors and therefor useful in the treatment of CO mediated disease states as well.

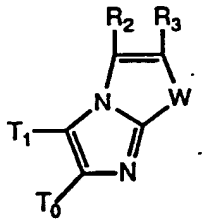
Another aspect of this invention relates to a method of treating an OPUFA mediated disease in a subject in need thereof which comprises administering to such subject an effective, OPUFA inhibiting amount of a compound of Formula (III). The compounds of Formula (III) are also effective cyclooxygenase inhibitors and therefor useful in the treatment of CO mediated disease states as well.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a method of using the compounds of Formula (I), as described above, for OPUFA mediated diseases comprising administration of an effective amount of a compound of Formula (I) to a mammal, including humans, in need thereof. Preferably the enzyme 5-lipoxygenase is inhibited. The invention further relates to a method of treating a cyclooxygenase pathway mediated disease, which process comprises administration of an effective amount of a compound of Formula (I) to a mammal, including humans, in need thereof.

This invention also relates to the novel compounds of Formula (II), described below and pharmaceutical compositions comprising a compound of Formula (II) and a pharmaceutically acceptable carrier or diluent. This invention also relates to a method of using the compounds of Formula (II) for treating OPUFA mediated disease, preferably by inhibition of the 5-lipoxygenase enzyme in a mammal, including humans, in need thereof. This invention also relates to a method of treating a cyclooxygenase pathway mediated disease comprising administration of an effective amount of cyclooxygenase pathway inhibiting amount of a compound of Formula (II) to a mammal, including humans, in need of such inhibition.

The compounds of Formula (II) are encompassed within the genus of the compounds of Formula (I) and are represented by the structure:



Formula (II)

wherein

W is -CR_5=CR_7-, -N=CR_7-, -S- or -O-;

R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

and one of T_1 and T_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when T_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of T_1 and T_0 is

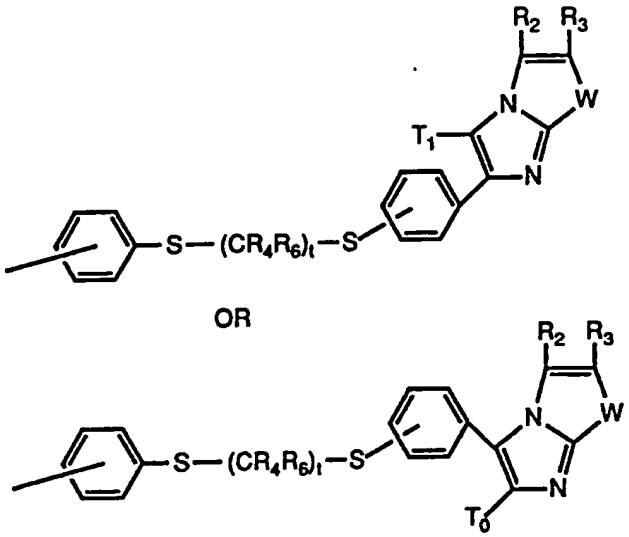
(a) monosubstituted phenyl wherein said substituent is hydroxy, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-C_{1-3} -alkanamido, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio , or Z; or

(b) disubstituted phenyl wherein one of said substituents is amino, N-C_{1-3} -alkanamido, N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(c) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, hydroxy, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio, or Z; or

(d) disubstituted phenyl wherein said substituents are, independently C_{1-3} alkylamino, C_{1-3} dialkylamino, amino, N-(C_{1-3}alkyl)-N-(C_{1-3} alkanamido, N-pyrrolidino or N-piperidino; or

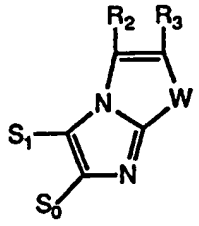
(e) a moiety of one of the following formulae:



OR

wherein t is 0 or 1;
R_4 and R_6 are independently selected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;
Z is $-S-(CR_4R_6)_t-S-Z_1$;
Z_1 is C_{1-9} alkyl, aryl or heteroaryl;
or a pharmaceutically acceptable salt thereof.

One aspect of this invention is use in medicine of the compounds of Formula (III), which are also encompassed within the genus of the compounds of Formula (I). The compounds of Formula (III) are useful as OPUFA inhibitors and in the treatment of CO mediated diseases, preferably by inhibition of the 5-LO and CO enzymes respectively. The compounds of Formula (III) are represented by the structure:



Formula (III)

wherein

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;
R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

and one of S_1 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when S_1 or S_0 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of S_1 and S_0 is

(a) monosubstituted phenyl wherein said substituent is -H, C_{1-4} alkyl, halo, C_{1-2} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, or acyloxyalkylthio; or

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, or C_{1-4} alkyl; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl; and the other is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, or acyloxyalkylthio: or

(d) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkylsulinfyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} -1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, or acyloxyalkylthio; or wherein the substituents together form a methylene dioxy;

and the pharmaceutically acceptable salts thereof.

Another aspect of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of Formula (III) for use in treating an OPUFA or CO pathway mediated disease state.

Another aspect of the present invention is a method of treating an OPUFA mediated disease state, in a mammal, including humans, in need of such treatment by administering an effective amount of a compound or pharmaceutically acceptable salt thereof selected from

2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]-imidazole;

5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or

5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole.

Preferaby the enzyme 5-lipoxygenase is inhibited.

Another aspect of the present invention is a method of treating a CO pathway mediated disease state, in a mammal, including humans, in need of such treatment, which process comprises administering, an effective amount of a compound or pharmaceutically acceptable salt thereof, selected from

2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]-imidazole;

5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or

5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole.

Yet another aspect of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound or pharmaceutically acceptable salt thereof, selected from 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]-imidazole; 5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or 5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole, for use in treating a CO or OPUFA pathway mediated disease.

Preferred OPUFA mediated disease states inhibited in the processes of the present invention, include, but are not limited to, arthritis, rheumatoid arthritis, osteoarthritis, allergic rhinitis, psoriasis, dermatitis, ischemic induced myocardial injury, reperfusion injury, gout, asthma, adult respiratory distress syndrome, atherosclerosis, inflammatory bowel disease, stroke, spinal cord injury and traumatic brain injury.

Preferred Cyclooxygenase mediated disease states inhibited in the processes of the present invention, include, but are not limited to, pyresis, pain, osteoarthritis, rheumatoid arthritis, thrombosis, inflammation, uticaria or edema.

The compounds of Formula (III) are described in a U.S. patent application by Bender et al., U.S.S.N. 07/365,349, filed June 13, 1989, and in Bender et al., PCT US90/03367, filed contemporaneously herewith, the entire disclosures all of which are hereby incorporated by reference. It has now been found that the compounds of Formula (III) possess the ability to inhibit both the 5-lipoxygenase and cyclooxygenase enzymes thereby making them useful for treating either a 5-LO or CO pathway mediated disease state in a mammal in need thereof.

A preferred embodiment of this invention for the compounds of Formula (I) is where W is $-CR_5=CR_7-$ or $-N=CR_7$.

Preferred compounds of Formula (I) include those wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is halo, C_{1-3} alkylamino, C_{1-3} dialkylamino, thiol, hydroxy, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, acyloxyalkylthio, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, acylthio, 1-acyloxy-1-alkylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio; or

(e) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkoxy, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group.

More preferred are the compounds of Formula (I) wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, acyloxyalkylthio, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, C_{1-3} alkylamino, or C_{1-3} dialkylamino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, acylthio, 1-acyloxy-1-alkylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio; or

(e) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkoxy, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or

1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group.

The most preferred compound of Formula (I) is 2-(4-Methoxyphenyl)-3-(4-pyridyl)-imidazo[1,2-a]-pyridine.

Other preferred compounds are:

2-(4-methoxyphenyl)-3-(4-(2-methyl)pyridyl)imidazo[1,2-a]pyridine;
2-(4-fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-dimethyl-alkylaminophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-methyl-aminophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-N-piperidinophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-acetoxymethylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-(2-acetylthio)phenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine;
2-(4-(2-acetylthio)phenyl)-3-(4-(2-methyl)pyridyl)imidazo[1,2-a]pyridine;
2-(4-pyridyl)-3-(4-methylsulfinyl)phenyl)imidazo[1,2-a]pyridine;
2-(4-pyridyl)-3-(4-methylthiophenyl)imidazo[1,2-a]pyridine;
2-(4-pyridyl)-3-(4-methylsulfinyl)phenyl)imidazo[1,2-a]pyridine;
6-(4-methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole;
6-(4-acetylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole;
6-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole;
7-(4-fluorophenyl)-6-(4-pyridyl)imidazo[1,2-a]pyrimidine;
7-(4-methylthiophenyl)-6-(4-pyridyl)imidazo[1,2-a]pyrimidine;
7-(4-methylsulfinylphenyl)-6-(4-pyridyl)imidazo[1,2-a]pyrimidine;
6-(4-methylthiophenyl)-5-(4-pyridyl)-imidazo[2,1-b]thiazole;
6-(4-methylsulfinylphenyl)-5-(4-[2-methyl]-pyridyl)-imidazo[2,1-b]thiazole;
6-(4-fluorophenyl)-3-(4-pyridyl)- imidazo[2,1-b]thiazole;
6-(4-N-pyrrolidinophenyl)-3-(4-pyridyl)-imidazo[2,1-b]thiazole;
6-(4-methoxyphenyl)-5-(4-(2-methyl)pyridyl)-imidazo[2,1-b]thiazole;
6-(4-acetylthiophenyl)-5-(4-(2-methyl)pyridyl)-imidazo[2,1-b]thiazole;
5-(4-acetylthiophenyl)-5-(4-pyridyl)-imidazo[2,1-b]thiazole;
5-(4-methylsulfinylphenyl)-6-(4-(2-methyl)pyridyl)-imidazo[2,1-b]thiazole; or
6-(4- dimethylalkylaminophenyl)-5-(4-(2-methyl)pyridyl)-imidazo[2,1-b]thiazole;

or a pharmaceutically acceptable salt of any one of the above compounds.

A preferred embodiment of this invention for the compounds of Formula (II) is where W is $-CR_5=CR_7-$ or $-N=CR_7$.

A preferred emodiment of the present invention are the compounds of Formula (II) wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-3} alkylamino, C_{1-3} dialkylamino, thiol, hydroxy, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} acylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio.

More preferred compounds of Formula (II) are those where

W is $-CR_5=CR_7-$, $-N=CR_7-$;

where one of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-3} dialkylamino or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylamino, or C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(c) disubstituted phenyl wherein one of said substituents is acylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio.

It should be noted that the compounds of Formula (I), (II) or (III) where R_1 or R_0 may be a C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} -2-alkenyl-1-sulfinyl, alkoxyalkylsulfinyl, and phenylsulfinyl moiety, are prodrugs which are reductively converted in vivo to the corresponding alkylthio or alkenylthio form.

By the term "halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo and iodo, preferably fluorine.

By the term "aryl" as used herein is meant phenyl, or naphthyl, which are both optionally substituted with halogen, C_{1-3} alkoxy, C_{1-3} alkylthio or C_{1-4} alkyl.

By the term "heteroaryl" as used herein is meant a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S; such as, but not limited, to quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole; all of which may be optionally substituted by one or more of halogen, C_{1-3} alkoxy, C_{1-3} alkylthio or C_{1-4} alkyl moieties.

By the term "OPUFA mediated disease or disease state" is meant any disease state which is mediated (or modulated) by oxidation of polyunsaturated fatty acids, specifically the arachidonic acid metabolic pathway. The oxidation of arachidonic acid by such enzymes as the lipoxygenase enzymes or cyclooxgenase enzyme is specifically targeted by the present invention. Such enzymes include, but are not limited to, 5-LO, 12-LO, 15-LO, and CO; which produce the following mediators, including but not limited to, PGE_2, LTB4, LTC4, LTD4, prostaglandins, thromboxane, and prostocyclin.

By the term "OPUFA interfering amount" is meant an effective amount of a compound of Formula (I) which shows a reduction of the in vivo levels of an oxgyenated arachidonic acid metabolite.

By the term "sulfinyl" as used herein is meant the oxide of the corresponding sulfide. By the term "thio" as used herein is meant the sulfide. For further clarification, the following table outlines the structural attachment of the atoms of the R_1 and R_0 substituents of the compounds of Formula (I):

Table 1

R_1 or R_0	Structural Attachment
C_{1-3} alkylsulfinyl	[AS(O)-]
C_{2-5} 1-alkenyl-1-thio	[AA^1C=CHS-]
C_{2-5} 1-alkenyl-1-sulfinyl	[AA^1C=CHS(O)-]
C_{3-5} 2-alkenyl-1-thio	[ACH=CA^1CH_2S-]
C_{3-5} 2-alkenyl-1-sulfinyl	[ACH=CA^1CH_2S(O)-]
1-acyloxy-1-alkylthio	[AC(O)OCH(A^1)S-]
acylthio	[DC(O)S-]
dithioacyl	[DC(S)S-]
thiocarbamyl	[DD^1NC(O)S-]
dithiocarbamyl	[DD^1NC(S)S-]
alkylcarbonylalkylthio	[DC(O)CH_2S-]
carbalkoxyalkylthio	[BOC(O)CH_2S-]
alkoxycarbonylthio	[BOC(O)S-]
alkoxythionothio	[BOC(S)S-]

alkoxyalkylthio	[$BOCH_2S$-]
alkoxyalkylsulfinyl	[$BOCH_2S(O)$]
alkylthioalkylthio	[$BSCH_2S$-]
disulfide [Z]	[-S-S-Z_1]

NOTE: A and A^1 are hydrogen or alkyl; and D and D^1 are hydrogen, C_{1-9} alkyl, or phenyl; B is C_{1-9} alkyl or aryl; and Z_1 is aryl, heteroaryl or C_{1-9} alkyl. The hydrogen atoms in the CH_2 groups described in Table 1 are, independently, optionally substituted by a C_{1-4} alkyl moiety.

Another aspect of the present invention is the novel oxidation of an aryl sulfide, in particular alkyl thio aryl function, such as a methylthiophenyl group, to the corresponding sulfoxide wherein the aryl sulfide is substituted on a heteroaromatic nitrogen containing ring system, such as imidazole, triazole, pyrimidine, pyridine, 6,7-dihydro-[5H]-pyrrolo[2,1-a]imidazole, 2,3-dihydroimidazo[2,1-b]-thiazole, imidazo[2,1-b]thiazole, imidazo[2,1-b]oxazole, imidazo[1,2-a]pyridine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, or a imidazo[1,2-a]pyrimidine ring system. The process occurs in high yield with minimal formation of the sulfone byproducts. This process oxidizes the sulfide in higher yields than do alternative methods, such as m-chloroperbenzoic acid. This process also utilizes the inexpensive and readily available reagents, potassium or sodium persulfate. This process also does not utilize toxic metal, thus providing advantages in purification of the reaction product and disposal of wastes.

Sodium and potassium persulfate are salts of peroxysulfuric acid. Other more commonly used peroxyacids, such as m-chloroperbenzoic acid, are well-known to oxidize amines and pyridines to their N-oxides. It would be the expectation, that persulfuric acid or its salts would exhibit similiar reactivity and hence make them useless for the oxidation of compounds such as those disclosed herein, as they contain several nitrogen atoms. Furthermore, sodium and potassium persulfate have been known for some time to oxidize aniline derivatives to aniline-o-sulfates (the Boyland-Sims oxidation, disclosed in Boyland et al., J. Chem. Soc. 3623 (1953), and in Berhman et al, J. Org. Chem. 43, 4551 (1978)) and to act as a co-oxidant in the oxidation of a wide variety of alkylamine to aldehydes or ketones (see Bacon et al., J. Chem Soc. (C), 1384 (1966). Srinivasan et al., Indian J. Chem., 268, p. 193 (1987) describes the oxidation of a number of sulfide compounds which have other functionalities such as methoxy, nitro, acetyl, and chloro groups but none contain an amine nitrogen, such as the compounds of this invention. The present invention has found that the persulfate reagents not only work on the compounds of Formula (I), (II) and (III) disclosed herein, but will also work well on their intermediates

and other ring systems which contain a heterocyclic nitrogen atom, such as pyridine, imidazole, or other tertiary amine moieties.

Prefered aryl sulfides are the phenylsulfide derivatives. Further preferred are the alkyl substituted alkyl sulfide derivatives, such as methyl or ethyl thio. Hetero-aromatic and non-aromatic nitrogen containing ring system on which the aryl sulfide moiety is found, includes but is not limited to pyrrole, pyrazole, imidazole, imidazolididine, pyrazolidine, pyrazoline, morpholine, pyridine, pyrazine, indolizine, indoline, purine, quinoline, isoquinoline, napthyridine, triazole, pyrimidine, piperidine, isoindole, 3H-indole, cinnoline, carbazole, phenanthradine, phenazine, isothiazole, imidazo[1,2-b][1,2,4]triazine, triazine, pyridazine, 6,7-dihydro-[5H]-pyrrolo-[2,1-a]imidazole, 2,3-dihydroimidazo[2,1-b]-thiazole-1-oxide or 1,1-dioxide, imidazo-[2,1-b]thiazole; 2,3,4,5 tetrahydro-imidazo[2,1-b]thiazole-1-oxide or 1,1-dioxide, imidazo[2,1-b]oxazole, imidazo[1,2-a]pyridine, 5,6,7,8-tetrahydroimidazo-[1,2-a]pyridine, or a imidazo-[1,2-a]pyrimidine ring system. The aryl sulfide groups in the case of multiple ring systems may be attached to either ring, saturated or unsaturated.

Preferrably the nitrogen heterocyclic ring system is imidazole, pyrole, 2,3-dihydroimidazo[2,1-b]-thiazole, imidazo[2,1-b]thiazole-1-oxide or 1,1-dioxide, imidazo[1,2-a]pyridine, 6,7-dihydro-[5H]-pyrrolo[2,1-a]imidazole or imidazole. The particulars of the oxidation are further described herein in the synthetic chemistry section.

More preferably is the oxidation of 2-(4-Methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole to the corresponding methylsulfonyl derivative Most preferred is the use of the oxidant sodium persulfate.

The preparation of 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo[1,2-a]imidazole; 5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]imidazole-7-ol; and 5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]imidazole is disclosed in Gallagher et al., Tetrahedron Letters, Vol. 30, No. 48, pp.6599-6602 (1989) the entire disclosure of which is hereby incorporated by reference. Preparation of the pharmaceutically acceptable salts of these three compounds can be prepared by known techniques such as the method of Bender et al., U.S. Patent 4,175,127, issued November 20, 1979, the disclosure of which is hereby incorporated by reference.

The preparation of all compounds of Formula (III) and the pharmaceutically acceptable salts thereof ,which are also encompassed within the Formula (I) genus described herein, when W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-; and R_2, R_3, R_5, and R_7 are independently H or C_{1-2} alkyl are prepared as described in U.S. patent application by Bender et al., U.S.S.N. 07/365,349, filed June 13, 1989, and in Bender et al., PCT US/90/03367, filed June 12, 1990 the entire disclosures all of which are hereby incorporated by reference.

The preparation of all compounds of Formula (II) and pharmaceutically acceptable salts thereof may be prepared by one skilled in the art using analogous methods readily available and adaptable to the ring systems described U.S. patent application by Bender et al., U.S.S.N. 07/365,349, filed June 13, 1989, and in Bender et al., PCT Serial PCT US/90/03367, filed June 12, 1990. Said analogous methods for synthesis of the particular substituent groups of Formula (II) are disclosed in Bender et al., U.S. Patent Number 4,175,127, issued November 20, 1979, Bender et al., U.S. Patent Application Serial Number 07/106,199 filed on July 10, 1987 or Bender et al., U.S. Patent Number 4,803,279, issued February 9, 1989, and in Adams et al., U.S. Patent 4,719,218, issued 01/12/88 the entire disclosures of all of which are hereby incorporated by reference.

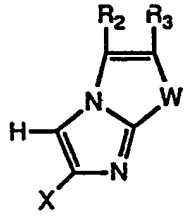
The preparation of all the remaining compounds of Formula (II) can be carried out by one of skill in the art according to the procedures outlined in the Examples, infra.

All the compounds of Formula (C), Formula (D), Formula (E), Formula (F), Formula (G) and Formula (H) are useful as intermediates in the preparation of the compounds of Formula (II). The preparation of all the compounds of Formula (C), Formula (D), Formula (E), Formula (F), Formula (G) and Formula (H) can be carried out by one of skill in the art according to the procedures outlined in the Examples, infra.

Pharmaceutically acceptable salts and their preparation are well known to those skilled in pharmaceuticals. Pharmaceutically acceptable salts of the compounds of Formula (I) or Formula (II) which are useful in the present invention include, but are not limited to, maleate, fumarate, lactate, oxalate, methanesulfonate, ethane-sulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate and phosphate salts. Preferred pharmaceutically acceptable salts of the compounds of Formula (I) or Formula (II) include hydrochloride and hydrobromide salts, and such salts can be prepared by known techniques such as the method of Bender et al., U.S. Patent 4,175,127, issued November 20, 1979.

The compounds of the present invention may contain 1 or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

The compounds of intermediate Formula (C) are represented by the structure:



FORMULA (C)

or a pharmaceutically acceptable salt thereof,

wherein:

W is -CR_5=CR_7-, -N=CR_7-, -S- or -O-;

R_2, R_3, R_5 and R_7 are, independently H or C_{1-2} alkyl;

X is a) 4-pyridyl or mono-C_{1-4}alkyl-substituted pyridyl; or

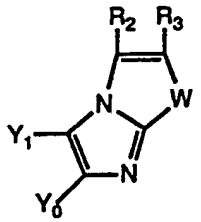
b) monosubstituted phenyl wherein said substituent is selected from halo, C_{1-3} alkoxy, hydroxy, C_{1-3} alkylthio, C_{1-4} alkyl, alkenylthio, phenylthio, alkoxyalkylthio, alkylthioalkylthio, C_{1-3} alkylamino, alkylcarbonylalkylthio, carbalkoxyalkylthio, C_{1-3} dialkylamino, CF_3, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-l-oxy or 2,2,2-trihaloethoxy;

(c) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-l-oxy, or hydroxy;

(d) disubstituted phenyl wherein said substituents are not the same and are independently selected from halo, C_{1-3} alkylamino, nitro, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(e) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, hydroxy, C_{1-3} alkylthio, 2,2,2-trihaloethoxy or prop-2-ene-1-oxy and the other substituent is independently selected from halo, C_{1-3} alkylamino, nitro, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino;

The intermediate compounds of Formula (D) are represented by the structure:



FORMULA (D),

or a pharmaceutically acceptable salt thereof,

wherein:

W is -CR_5=CR_7-, -N=CR_7-, -S- or -O-;

R_2, R_3, R_5 and R_7 are, independently, -H or C_{1-2} alkyl;

Y_1 is 4-(1,4-dihydro)pyridyl substituted with N-(C_{1-8} alkanoyl), N-(C_{1-8} alkoxycarbonyl), N-benzoyl, N-phenoxycarbonyl, N-phenylacetyl, or N-benzyloxy-carbonyl;

Y_0 is (a) monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, hydroxy, alkenylthio, phenythio, alkoxyalkylthio, alkylthioalkylthio, alkylcarbonylalkylthio, carbalkoxy-alkylthio, C_{1-3} dialkylamino, CF_3, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, or 2,2,2-trihaloethoxy;

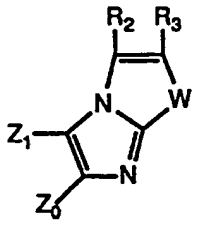
(b) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylthio, alkenylthio, phenylthio, alkoxyalkylthio, alkylthioalkylthio, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, or hydroxy; or wherein the substitutents together form a methylene dioxy group; or

(c) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(d) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, hydroxy, C_{1-3} alkylthio, 2,2,2-trihaloethoxy or prop-2-ene-1-oxy and the other substituent is independently selected from halo, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino or N-piperidino; or

(e) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, halo, C_{1-3} dialkylamino, and the other is selected from alkenylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio,

The intermediate compounds of Formula (E) are represented by the structure:



FORMULA (E),

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5 and R_7 are, independently, -H or C_{1-2} alkyl;

one of Z_1 and Z_0 is 4-(1,2-dihydro-2-alkyl)pyridyl substituted with N-(C1-8 alkanoyl), N-(C1-8 alkoxycarbonyl), N-benzoyl, N-phenoxycarbonyl, N-phenylacetyl, or N-benzyloxycarbonyl; and the other of Z_1 and Z_0 is

(a) monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkoxy, halo, C_{1-4} alkyl, C_{1-3} alkylthio, alkenylthio, phenylthio,

alkoxyalkylthio, alkylthioalkylthio, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, CF_3, N-pyrrolidino, N-piperidino, prop-2-ene-l-oxy or 2,2,2-trihaloethoxy;

(b) disubstituted phenyl wherein said substitutents are independently selected from C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido),C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino;

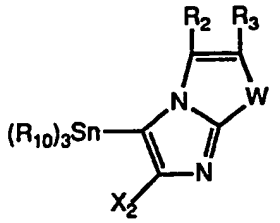
(c) disubstituted phenyl wherein said substitutents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} dialkylamino, C_{1-3}alkylthio, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy,or prop-2-ene-l-oxy, alkenylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio; or wherein the substitutents together form a methylene dioxy group;

(d) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, C_{1-3} alkylthio, 2,2,2-trihaloethoxy or prop-2-ene-1-oxy and the other substituent is independently selected from halo, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino;

(e) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, halo, or C_{1-3} di-alkylamino, and the other substituent is selected from alkenylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio;

or a pharmaceutically acceptable salt thereof.

The intermediate compounds of Formula (F) are represented by the structure:



FORMULA (F)

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5 and R_7 are, independently, -H or C_{1-2} alkyl;

R_{10} is C_{1-4} alkyl; and

X_2 is 4-pyridyl or mono-C_{1-4}alkyl-substituted pyridyl;or

(a) monosubstituted phenyl wherein said substituent is selected from fluoro, chloro, C_{1-3} alkoxy, C_{1-4} alkyl, C_{1-3} alkylthio, alkenythio, phenylthio, alkoxyalkylthio, alkylthioalkylthio, C_{1-3} dialkylamino, CF_3, C_{1-3} alkylamino, N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy or 2,2,2-trihaloethoxy;

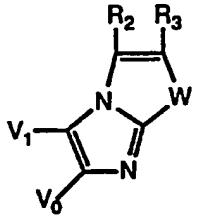
(b) disubstituted phenyl wherein said substituents are the same and are selected from fluoro, chloro, C_{1-3} alkoxy, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, alkenythio, phenylthio, alkoxyalkylthio, alkylthioalkylthio;

(c) disubstituted phenyl wherein said substituents are independently selected from fluoro, chloro, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(d) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, 2,2,2-trihaloethoxy or prop-2-ene-1-oxy and the other substituent is independently selected from fluoro, chloro, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino or N-piperidino; or

e) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, fluoro, chloro, C_{1-3} alkylamino, or C_{1-3} dialkylamino, and the other is selected from alkenythio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio.

The intermediate compounds of Formula (G) are represented by the structure:



FORMULA (G),

or a pharmaceutically acceptable salt thereof,

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

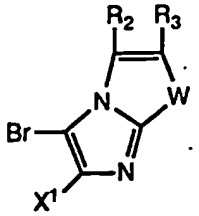
R_2, R_3, R_5 and R_7 are, independently, -H or C_{1-2} alkyl; and

one of V_1 or V_0 is 4-pyridyl or C_{1-4}alkyl-4-pyridyl, provided that when V_1 is C_{1-4}alkyl-4-pyridyl the alkyl substitutent is located at the 2-position of the pyridine ring, and the other of V_1 and V_0 is selected from:

(a) monosubstituted phenyl wherein said substituent is mercapto; or

(b) disubstituted phenyl wherein one of said substituents must be mercapto and the other is selected from mercapto, C_{1-3} alkoxy, halo, nitro, C_{1-4} alkyl, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, C_{1-3} alkanamido, N-C_{1-3} -alkyl-C_{1-3}alkanamido, C_{1-3} dialkylamino, N-pyrrolidino or N-piperidino;

The intermediate compounds of Formula (H) are represented by the structure:



FORMULA (H)

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5 and R_7 are, independently, -H or C_{1-2} alkyl; and

X^1 is selected from

(a) monosubstituted phenyl wherein said substituent is selected from fluoro, chloro, C_{1-3} alkoxy, C_{1-4} alkyl, C_{1-3} dialkylamino, CF_3, C_{1-3} alkylamino, N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, C_{1-3} alkylthio, alkenylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio;

(b) disubstituted phenyl wherein said substituents are the same and are selected from fluoro, chloro, C_{1-3} alkoxy, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, C_{1-3} alkylthio, alkenylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio ;

(c) disubstituted phenyl wherein said substituents are independently selected from fluoro, chloro, C_{1-3} alkylthio, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

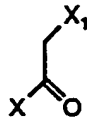
(d) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, 2,2,2-trihaloethoxy or prop-2-ene-1-oxy and the other substituent is independently selected from fluoro, chloro, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino;

(e) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkoxy, fluoro, chloro or C_{1-3} dialkylamino; and the other substituent is independently selected from alkenylthio, C_{1-3} alkylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio ;

or a salt thereof.

Additional intermediate compounds which are also useful in the process of this invention to make the compounds of Formula (II) are compounds of Formulas (IIa) and (IIb) as described below. Additionally, as more elaborately described herein, while all of the compounds of Formula (II) are useful in the method of the subject invention, some of the compounds of Formula (II) are also useful as intermediates in the preparation of other compounds of Formula (II).

As used herein in the Synthesis Examples, the term "Formula (A)" refers to a compound of the formula:



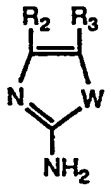
FORMULA (A)

wherein:

X is chosen from a group consisting of mono or disubstituted phenyl as defined in Formula (C), 4-pyridyl and mono-C_{1-4}alkyl-substituted-4-pyridyl; and

X_1 is a halogen such as Cl or Br.

As used herein in the Synthesis Examples, the term "Formula (B)" refers to a compound of the formula:



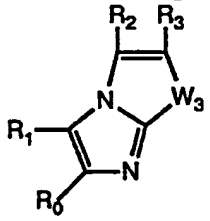
FORMULA (B)

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-; and

R_2, R_3, R_5 and R_7 are, independently, -H or C_{1-2} alkyl.

The compounds of Formula (IIa) are represented by the strucutre:



Formula (IIa)

wherein:

W_3 is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

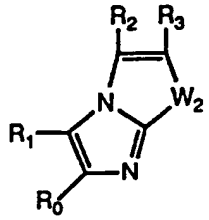
R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

and one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-3} alkylsulfinyl;

(b) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl; and the other is selected from C_{1-3} alkylsulfinyl, C_{1-4} alkyl, nitro, N-C_{1-3} -alkanamido, N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), C_{1-3} dialkylamino, N-pyrrolidino,N-piperidino, halo, C_{1-3} alkoxy, 2,2,2-trihaloethoxy, or prop-2-ene-1-oxy.

As used herein in the Synthesis Examples, the term "Formula (IIb)" refers to a compound of the formula:



FORMULA (IIb)

wherein:

W_2 is -CR_5=CR_7-, -N=CR_7-, -S- or -O-;

R_3, R_5, R_7 and R_9 are, independently, H or C_{1-2} alkyl;

One of R_1 or R_0 is 4-pyridyl and the other is selected from:

(a) phenyl or monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, alkenylthio, phenylthio, alkoxyalkylthio, alkylthioalkylthio, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido),C_{1-3} dialkylamino, CF_3, N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, alkylcarbonylalkylthio, carbalkoxyalkylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio; or

(b) disubstituted phenyl wherein said substitutents are independently selected from N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino;

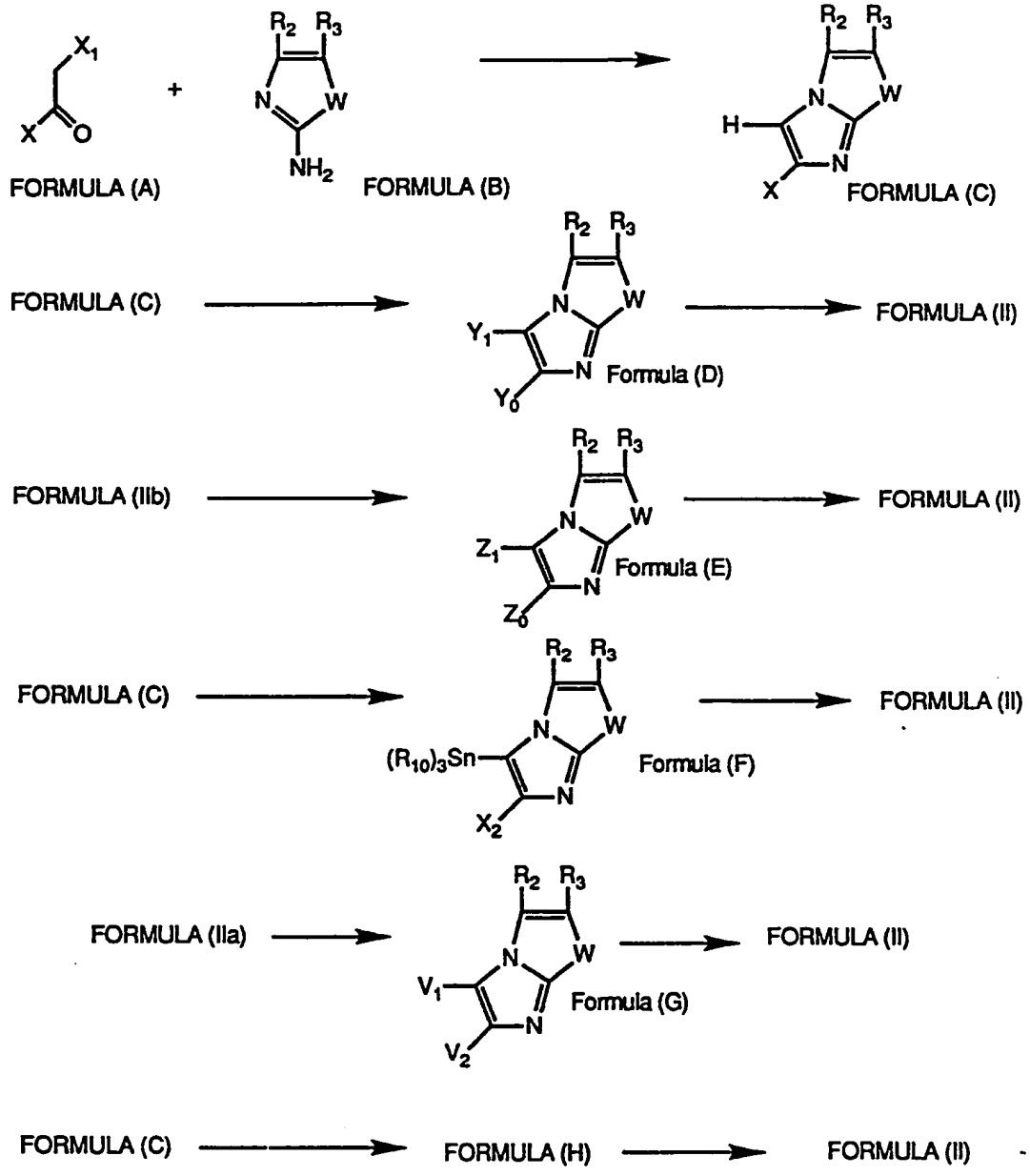
(c) disubstituted phenyl wherein said substitutents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} dialkylamino, C_{1-3} alkylthio, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, hydroxy, alkylcarbonylalkylthio, carbalkoxyalkylthio, phenylthio, alkoxyalkylthio, or alkylthioalkylthio;

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylthio, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; and the other substituent is selected from C_{2-5}-1-alkenyl-1-thio, C_{3-5}-2-alkenyl-1-thio, phenylthio, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxyalkylthio, or alkylthioalkylthio;

or a salt thereof.

The compounds of Formula (II) can be prepared according to the following Scheme 1:

SCHEME 1



All the necessary 1-aryl-2-halo-ethanone Formula (A) compounds wherein X_1 is a halogen such as Cl or Br and X is chosen from a group consisting of mono or disubstituted phenyl, 4-pyridyl, and alkyl-substituted 4-pyridyl, are known in the art or are prepared by treatment of the correspondingly substituted 1-phenylethanones or 1-(4-pyridyl)ethanones (which are commercially available or known in the art) with one equivalent of halogen, preferably bromine, in acetic acid, 48% hydrobromic acid, or a halocarbon solvent such as chloroform. See, e.g., Langley, Org. Syn. Coll., 1, 127 (1944) and Taurins et al., J. Heterocyclic Chem., 7, 1137 (1970). Alternatively, the mono and disubstituted 1-phenyl-2-chloro-ethanone Formula (A) compounds can be prepared by Friedel Crafts acylation of the corresponding mono or disubstituted benzenes with 2-chloroacetyl chloride and aluminum chloride by the method of Joshi et al., J. Heterocyclic Chem., 16, 1141 (1979). By these methods, Formula (A) compounds are prepared wherein X is 4-pyridyl, mono-C_{1-4}alkyl-substituted pyridyl, monosubstituted phenyl (as defined in Formula (C); or disubstituted phenyl (as defined in Formula (C)).

Compounds of Formula (C) as defined above are prepared from the following classes of Formula (B) compounds wherein R_2, R_3, R_5, or R_7 are hydrogen or are one or more C_{1-2} alkyl groups; i.e.,:

1. 2-amino-(1,3)-oxazole (W= O);
2. 2-amino-(1,3)-thiazole (W= S);
3. 2-aminopyridine (W= -(C-R_5)=(C-R_7)-),; and
4. 2-aminopyrimidine (W= -(N=CR_7)-)

The necessary Formula (B) compounds are commercially available or are known in the art and can be readily prepared by one of skill in the art.

The Formula (B) compound is reacted with a 1-aryl-2-halo-ethanone Formula (A) compound to afford the Formula (C) compound by alkylation followed by cyclodehydration. In this way, the following classes of Formula (C) compounds are prepared:

1. imidazo[2,1-b]oxazole (W= O);
2. imidazo[2,1-b]thiazole (W= S);
3. imidazo[1,2-a]pyridine (W= -(C-R_5)=(C-R_7)-);
4. imidazo[1,2-a]pyrimidine (W= -(N=CR_7)-)

The reaction to form the Formula (C) compounds is performed in a nonpolar solvent such as chloroform or toluene, or in a polar nonprotic solvent such as dimethylformamide or acetonitrille. Alkylation is facilitated by the presence of one to four equivalents of a base such as powdered sodium carbonate or triethylamine, and cyclodehydration is facilitated by heating (between ambient temperature and reflux) or removing the solvent and refluxing the residue in water or dilute aqueous acid.

Compounds of Formula (C) may be treated with an alkyllithium compound to yield the corresponding lithium reagent by metallation. The lithium intermediate may then be treated with an excess of magnesium halide or zinc halide etherate to yield the corresponding organometallic reagent by transmetallation. To this organometallic reagent a 4-bromo, 4-iodopyridine or the triflate ester of a 4-hydroxy pyridine (a 4-trifluoromethyl-sulfonyloxypyridine)is added in the presence of a palladium (O) catalyst, such as tetrakis(triphenyl-phosphine)-palladium, with hexamethyl-phosphoramide; or with a palladium (II) catalyst, such as $PdCl_2$(1,4-bis(diphenylphosphino)-butane) catalyst , optionally, in the presence of lithium chloride and a base,such as triethylamine, to yield the corresponding Formula (II) compounds. [See Kumada et al., Tetrahedron Letters, 22, 5319 (1981).]

Compounds of Formula (F) as defined above are intermediates to the corresponding Formula (II) compounds and are prepared by metallation of the appropriate Formula (C) compounds, where X is 4-pyridyl or monoalkyl-substituted 4-pyridyl, with a lithiating agent (such as s-butyllithium or n-butyllithium) in an ethereal solvent (such as tetrahydrofuran), followed by treatment with a trialkyltin halide. These Formula (F) compounds are employed to prepare the Formula (II) compounds where R_Q is 4-pyridyl or monoalkyl-substituted 4-pyridyl, i.e., one mole equivalent of the Formula (F) compound is added to an excess of a solution of a mono- or di-substituted phenyl bromide, triflate, or preferably the iodide, in an inert solvent (such as tetrahydrofuran) preferably containing 10% hexamethyl-phosphoramide(HMPA) and 1 to 10 mole percent of a palladium (0) catalyst (such as tetrakis(triphenylphosphine)-palladium) by the method described in Adams et al., U.S. Patent 4,719,218, issued 01/12/88 and in Adams et al., U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988 now U.S. Patent Number 5,002,942, issued March 26, 1991, or by using a palladium (II) catalyst in the presence of lithium chloride and an added base such as triethylamine. Triflate precursors are prepared from the corresponding substituted phenols by treatment with trifluorosulfonic anhydride in the presence of a base such as pyridine or triethylamine.

The compounds of Formula (II) wherein either R and R_Q are a 4-alkyl substituted pyridyl are also prepared by this route. Alternatively, compounds of Formula (II) may be prepared by the analogous reaction of an aryl or heteroaryl trialkyltin compound with a mixture of a Formula (H) compound and tetrakis-(triphenylphosphine)-palladium under similar conditions. The reaction conditions for Formula (F), and (H) compounds require that the substituent amino and sulfur substituted compounds, for example, be non-oxidized, or protected, i.e. N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), etc., hence the final products of these reactions are all optionally subject to additional oxidation/acylation, etc. procedures. For use herein, when a compound of Formula (C) contains X as a phenyl

(mono- or di- substiuted), the phenyl must be substituted with other than hydroxy, bromine, or iodine to yield a compound of Formula (H).

The compounds of Formula (C) may also be treated with an excess of bromine to yield a bromo derivative, (a compound of Formula (H)) wherein the substituent group on the phenyl of a Formula (C) compound is substituted with other than an iodine, bromine, hydrogen, hydroxy or nitro substituent group, and is added to a pyridine boronic acid [$B(OH)_2$ -4-pyridyl] with a palladium catalyst such as $Pd(Ph_2P(CH_2)_4$- $PPh_2)Cl_2$ or $Pd(PPh_3)_4$ in the presence of about three equivalents of sodium bicarbonate for about 12 hours under reflux conditions with a DME (dimethyl ethane)/H_2 in a 3:1 ratio. The pyridine-4-boronic acid is prepared from 4-bromopyridine by reation with n-butyllithium, trapping of the anion with triethyl borate and acid hydrolysis of the boronate ester. The method is similiar to that of Fischer and Haviniga, Rec. Trav. Chim. pays Bas, 84, 439 (1965). Additional references for coupling of bromopyridines with boronic acids are Snieckus,V., Tetrahedron Lett., 29, 2135 (1988) and Terashimia, M., Chem. Pharm. Bull., 11, 4755 (1985).

The brominated Formula (C) compound (Formula (H) compound) can also, following halogen-metal exchange with n-BuLi and transmetallation with $MgBr_2$, be coupled to a substituted halobenzene, preferably an iodide in the presence of bidentate palladium (II) catalyst or a $Ni(II)Cl_2$ (1,2-bi-diphenyl-phosphino)ethane) catalyst to yield the desired regioisomer of the compounds of Formula (II). [See, Pridgen, J. Org. Chem., 47, 4319 (1982)].

The magnesium or zinc derivative of a Formula (C) compound, however derived, when X is other than a 4-mono C_{1-4} alkylpyridyl or 4-pyridyl may also be coupled to a substituted 4-halopyridine in the presence of the noted palladium (II) or Ni (II) catalyst to yield the final desired compounds of Formula (II).

Compounds of Formula (II) where R is phenyl or substituted phenyl, and R^1 is 4-pyridyl are preferably prepared in two steps by a modification of the method of Lantos et al., European Patent Application No. 203,787 published March 12, 1986, the disclosure of which is herein incorporated by reference.

Compounds of Formula (D), as defined above, are N-(substituted carbonyl)-1,4-dihydropyridines. The Formula (D) compounds are prepared by treatment of the corresponding Formula (C) compounds of classes 1, 2,3,and 4 described above, with a substituted carbonyl pyridinium salt by the method of Bender et al., U.S. Patent 4,803,279, issued February 9, 1989; Adams et al., U.S. Patent 4,719,218, issued 01/12/88 and in Adams et al., U.S. Patent Number 5,002,942, issued March 26, 1991. The pyridinium salt may be either preformed or preferably prepared in situ by addition of the substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or preferably an alkyl haloformate ester, such as acetyl bromide,

benzoylchloride, benzyl chloroformate, or preferably ethyl chloroformate) to a solution of the Formula (C) compound in pyridine or in an inert solvent such as methylene chloride to which pyridine has been added.

Compounds of Formula (E), as defined above, serve as intermediates in the preparation of Formula (II) compounds where one of R_0 or R_1 in the product Formula (II) compound is mono-alkyl substituted pyridyl. Compounds of Formula (E) are N-(substituted carbonyl)-4-(1,2-dihydro-2-alkyl)pyridines and are prepared by the method of Comins et al., J. Org. Chem., 47, 4315 (1982), i.e., by treatment of an appropriate Formula (IIb) compound in a dry ethereal solvent such as tetrahydrofuran at reduced temperature (below 0°C) with a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or preferably an alkyl haloformate ester), followed by treatment with an alkyl grignard reagent.

Compounds of Formula (D) and Formula (E) serve as intermediates in the preparation of the compounds of Formula (II) and are converted into compounds of Formula (II) by deacylation and oxidation with a mild oxidizing agent by the methods described in Bender et al., U.S. Patent No. 4,803,279; Adams et al., U.S. Patent 4,719,218, issued 01/12/88 and in Adams et al., U.S. Patent Number 5,002,942, issued March 26, 1991. Exemplary oxidation systems are sulfur in a refluxing inert solvent, or solvent mixture (such as decalin, decalin and diglyme, p-cymene, xylene, mesitylene), or preferably with potassium tert.-butoxide in tert.-butanol with O_2 gas at reflux for 15 minutes to the afford the corres-ponding compound of Formula (II). The compounds of Formula (II) may now be optionally reduced, hydrolyzed, oxidized, demethylated, or acylated to produce other desired Formula (II) compounds produced by this synthetic route.

Regioisomers of Formula (II) compounds where R_1 is substituted phenyl, or 4-pyridyl and R_0 is 4-pyridyl are obtained from compounds of Formula (C) where X is 4-pyridyl. Compounds of Formula (C) where X is 4-pyridyl or 2-alkyl-4-pyridyl are prepared by treatment of an alkyl substituted or unsubstituted 4-bromoacetylpyridine hydrobromide salt of Formula (A), wherein R is 4-pyridyl or 2-alkyl-4-pyridyl [prepared as described by Taurins et al., J. Het Chem., 7, 1137 (1970)] with 2-3 equivalents of the 2-aminopyrrole or 2-aminopyridine by the procedure used to prepare the other compounds of Formula (C) described above. Bromination, by the procedure of Kano cited above, affords the corresponding Formula (H) compounds, as previously described. Metallation of the Formula (C) compounds with n-BuLi or halogen-metal interchange of the Formula (H) compounds with n-BuLi, followed by transmetallation with $MgBr_2$ and coupling to the substituted halobenzene, preferably iodobenzene, or 4-halopyridine, preferably where halo is iodo, in the presence of the bidentate phosphine-palladium or nickel complex as described above affords the desired regioisomers of Formula (II). Alternatively the

metallated pyridine or substituted benzene may be coupled to the Formula (H) compounds employing the catalysts as described above.

Compounds of Formula (II) where one of R_1 or R_0 is mono or disubstituted phenyl possessing a 4-halogen substituent (preferably fluoride) can be converted to the 4-alkylthio Formula (II) compound by displacement of the halide ion with approximatetly 1.2 equivalents of the sodium salt of the metal alkyl-mercaptide salt (such as sodium thioethoxide), or arylmercaptan, in a polar nonprotic solvent (such as dimethyl-formamide) heated to between 70 and 150°C.

Compounds of Formula (G) possessing one or more mercapto functionalities are prepared via Pummerer Rearrangement on the corresponding alkylsulfinyl-substituted compounds of Formula (IIa). Pummerer Rearrangement of the corresponding compounds of Formula (IIa) is accomplished by the method described in Adams et al., U.S. Patent Number 5,002,942, issued March 26, 1991 by refluxing with an alkanoic acid anhydride. The compounds of Formula (C) may also be used to make the analagous compounds of Formula (G) containing a hydrogen in the V_1 position. Such use of the Formula (C) compounds wherein the alkylthio group is oxidized to an alkylsulfinyl function and then reacted in the similiar manner as the Formula (IIa) compounds described herein to yield the corresponding mercapto substituted Formula (C) compounds, which may in turn be used to prepare the various other Formula (C) compounds, such as alkoxyalkylthio, alkenylthio, alkylthioalkylthio, alkylcarbonylalkylthio, or carbalkoxyalkylthio functions.

The Formula (G) compounds where one of V_1 or V_0 is a mono or di-substituted phenyl having at least one mercapto substituent are obtained by hydrolysis of the Formula (II) acyloxyalkylthio products or preferably by treatment of a Formula (IIa) compound with trifluoroacetic anhydride followed by basic solvolysis with a base such as sodium methoxide in methanol, similar to the method of R. N. Young et al., Tetrahedron Letters, 25, 1753 (1984).

Formula (G) compounds serve as intermediates for the synthesis of Formula (II) compounds where one of R_1 or R_0 of the Formula (II) compound is mono or disubstituted phenyl having at least one 2-alkenyl-1-thio function. A solution of the Formula (G) intermediate in a polar solvent such as dimethylformamide is treated with a base, preferably a metal hydride such as sodium hydride, and the sodium mercaptide salt formed is treated with a 1-halo-2-alkene such as allyl bromide and heated from 25 to 80°C to give the Formula (II) compounds where one of R_1 or R_0 is a disubstituted phenyl having at least one 2-alkenyl-1-thio substituent.

The Formula (G) compounds described above also serve as intermediates for the synthesis of Formula (II) compounds in which one of R_1 or R_0 is a di-substituted phenyl having at least one 1-alkenyl-1-thio function. Treatment of the Formula (G) compound in a nonprotic solvent such as tetrahydrofuran with a strong base such as lithium

diethylamide at low temperature (-78 to -20°C) generates the lithium mercaptide salt. This salt is alkylated at 0°C with a trimethylsilyl-methylating agent (such as trimethylsilylmethyl halide, triflate, or acetate) to form the trimethylsilylmethylthio substituent. The latter is deprotonated with addition of another molar equivalent of lithium diethylamide and treated with an aldehyde or ketone to give the Formula (II) compound where V_0 or V_1 is a di-substituted phenyl having at least one 1-alkenyl-1-thio substituent.

Compounds of Formula (II) where one of R_1 or R_0 is mono or disubstituted phenyl possessing a 4-halogen substituent (preferably fluoride) can be converted to the 4-alkylthio Formula (II) compound by displacement of the halide ion with a metal alkyl-mercaptide salt (such as sodium thioethoxide) in a polar nonprotic solvent (such as dimethylformamide) heated to between 70 and 150°C.

The Formula (G) compounds may be obtained by treatment of a Formula (II) or (III) compounds containing a halophenyl function, preferably a fluoro or bromophenyl, having at least one halo substituent on the phenyl ring, in dimethyl sulfoxide (DMSO) with NaSH(sodium bisulfide). An alternative reaction to yield a Formula (C) compound containing a substituted phenyl wherein one of the substituents is a mercapto function, or a Formula (G) compound is to treat a halophenyl derivative of Formula (II), or (C) with the sodium salt of an alkylmercaptan with catalytic amount of a palladium (O) compound, such as tetrakis(triphenylphosphine)-palladium in a solvent, such as DMSO.

Compounds of Formula (I) or (II) wherein R or R^1 is a mono- or di-substituted phenyl having at least one C_{1-3}alkylsulfinyl, C_{1-3}alkylsulfonyl, or C_{1-3} alkenylsulfinyl, or compounds of Formula (II) wherein R or R^1 is a di-substituted phenyl having at least one C_{1-3}alkylsulfinyl, C_{1-3}alkylsulfonyl, or C_{1-3}alkenylsulfinyl; or R or R^1 is a mono- or di-substituted phenyl having at least one alkoxyalkylsulfinyl or phenyl-sulfinyl substituent are prepared by treatment of one or more equivalents of the corresponding compound of Formula's (I), (II) or (III) wherein R or R^1 are C_{1-3} alkylthiophenyl, C_{1-3} alkylsulfinylphenyl, acyloxyalkylthiophenyl, alkoxyalkylthio, phenylthio, or alkenylthiophenyl with one or more equivalents of an oxidizing agent (such as 3-chloroperbenzoic acid in an inert solvent or sodium or potassium persulfate in an aqueous organic acid, such as acetic acid, or sodium periodate in peroxide, a polar solvent such as aqueous methanol containing a mineral acid such as hydrochloric acid), aqueous acetic acid, per mercapto function, in an inert solvent. Compounds of Formula (II) wherein R or R^1 are C_{1-3} alkyl-sulfonyl, alkenyl-sulfonyl or alkenyl-sulfinyl substituted phenyl are prepared by treatment of one equivalent of the corresponding C_{1-3} sulfinyl Formula (II) compound with 2/3 equivalent of $KMnO_4$ per sulfinyl function in aqueous acid solution by the method of Chatterway et al., J. Chem. Soc. 1352 (1930), or alternatively with one equivalent of a peracid.

Compounds of Formula (II) possessing an alkylsulfinyl, 1-alkenyl-1-sulfinyl, or 2-alkenyl-1-sulfinyl mono or disubstituted phenyl ring, or those compounds of Formula (II) prepared by oxidation of the corresponding compounds of Formula (IIa) (possessing, respectively, an alkylthio, 1-alkenyl-1-thio or 2-alkenyl-1-thio mono or disubstituted phenyl ring by employing one equivalent of oxidizing agent per sulfide in the molecule can be produced by use of an oxidizing agent as well. The oxidizing agent may be an organic peracid (such as 3-chloroperoxybenzoic) added dropwise to a solution of the Formula (II) compound in a halocarbon (such as methylene chloride) at ice bath temperature, or an inorganic agent (such as sodium periodate, sodium persulfate, potassium persulfate, or hydrogen peroxide) in aqeuous acetic acid, or acetic acid, added dropwise to a solution of the Formula (II) compound in water containing 2 equivalents of an inorganic acid (such as hydrochloric acid).

Applicant's have found as one aspect of this invention the use of the oxidizing agents, sodium persulfate and potassium persulfate for producing aryl sulfoxides from arylsulfides on nitrogen containing heterocyclic ring systems. This is a process which comprises treating said aryl sulfide with sodium or potassium persulfate in aqeuous acetic acid yielding the corresponding arylsulfoxide. As noted previously, Srinivasan et al., Indian J. Chem., 268, p. 193 (1987) describes the oxidation of a number of sulfide compounds which have other functionalities such as methoxy, nitro, acetyl, and chloro groups but none contain an amine nitrogen such as the compounds of this invention. It is in fact the oxidation of such moieties while attached to such hetero nitrogen ring systems that is unusual as the expectation that the nitrogen would themselves be oxidized. Applicants show herein that the arylsulfides, particularly the alkylthiophenyl moieties can safely be oxidized to the corresponding sulfones in the presence of a hetero-nitrogen containing ring system.

The reaction temperatures may be quite varied and ranger from about 0° C to about 100° C. Preferably the temperature range is from about 0° C to about 60° C. The reaction time may be from minutes to days, and an additional co-solvent may also be used. Such co-solvents include, but are not limited to, THF (tetrahydrofuran) and acetone. The method of mixing need not be in a dropwise fashion as indicated above for other oxiziding agents.

Prefered aryl sulfides are the phenylsulfide derivatives. Further preferred are the alkyl substituted alkyl sulfide derivatives, such as methyl or ethyl thio. Hetero-aromatic and non-aromatic nitrogen containing ring system on which the aryl sulfide moiety is found, includes but is not limited to, imidazole, triazole, pyrrole, pyrimidine, pyridine, 6,7-dihydro-[5H]-pyrrolo[2,1-a]imidazole, pyrrolo[2,1-a]imidazole; 2,3-dihydroimidazo[2,1-b]-thiazole, imidazo[2,1-b]thiazole--oxide or 1,1-dioxide; 2,3,4,5, tetrahydro-imidazo[2,1-b]thiazole-1-oxide or 1,1-dioxide, imidazo[2,1-b]oxazole,

imidazo[1,2-a]pyridine, 5,6,7,8-tetrahydroimidazo-[1,2-a]pyridine; 1,4-dihydroypyridinyl; 1,2,5,6-tetrahydropyridininyl, or a imidazo-[1,2-a]pyrimidine ring systems. The aryl sulfide in the case of multiple ring systems may be attached to either ring.

Preferrably the nitrogen heterocyclic ring system is 2,3-dihydroimidazo[2,1-b]-thiazole, imidazo[2,1-b]thiazole-1-oxide or 1,1-dioxide, imidazo[1,2-a]pyridine, 6,7-dihydro-[5H]-pyrrolo[2,1-a]imidazole or imidazole.

Acetophenones substituted with a mono- or di-substituted phenyl having at least one N-(C_{1-3}alkanamido)or N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), and in some cases the Formula (C), and Formula (II) compounds, are prepared by acylation of the corresponding amino and N-(C_{1-3} alkylamino) compounds with the alkanoic acid anhydride or chloride in pyridine. Another alternative preparation of the N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido) phenyl substituted Formula (C) and Formula (II) compounds is the alkylation of the corresponding N-(C_{1-3} alkanamido) substituted compounds with sodium hydride and a C_{1-3} alkyl bromide or iodide in dimethylformamide.

Formula (C) and Formula (II) compounds containing a mono- or di-substituted phenyl having at least one amino substituent are prepared either by hydrolysis of the corresponding N-(C_{1-3} alkanamido) compounds in refluxing 6 N mineral acid or by catalytic reduction of the corresponding nitro compounds.

Formula (C) and Formula (II) compounds containing a mono- or di-substituted phenyl having at least one N-(C_{1-3} alkylamino) substituent are preferably prepared by acid catalyzed hydrolysis of the corresponding N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido) compounds of Formula (C) and Formula (II), respectively, prepared as described above for the aminophenyl substituted compounds, or alternatively, either by (a) reduction of the corresponding N-(C_{1-3} alkanamido) compounds with borane or borane dimethylsulfide complex in THF by the method of Brown, "Organic Synthesis via Boranes", John Wiley and Sons, (1975), or (b) by cleavage of the corresponding N,N-(di C_{1-3} alkylamino)phenyl substituted Formula (C) and Formula (II) compounds with cyanogen bromide in the Von Braun reaction [see, Hageman Org. Reactions, Vol. 7, 198 (1953)].

Formula (C) and Formula (II) compounds containing a mono- or di-substituted phenyl having at least one N,N-(di C_{1-3} alkylamino) substituent are alternatively prepared either by reduction of the corresponding N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido) compounds of Formula (C) and Formula (II) with borane as described above for the N-(C_{1-3} alkylamino) substituted compounds, or by displacement of the bromide by a N,N-dialkylamine in the corresponding 4-bromo-3-nitrophenyl Formula (C) and Formula (II) compounds by heating at 140°C with the N,N-dialkylamine and potassium carbonate in an inert solvent.

Formula (C) and Formula (II) compounds containing a mono- or di-substituted phenyl having at least one N-pyrrolidino and N-piperidino substituent are alternatively prepared by cyclodialkylation of the corresponding aminophenyl compounds with dibromobutane or dibromopentane and anhydrous potassium carbonate in an inert solvent such as dimethylformamide.

Compounds of Formula (C) where X is mono- or di- substituted phenyl having at least one 2,2,2-trihaloethoxy or prop-2-ene-1-oxy substituent are prepared by alkylation of the appropriate phenols of Formula (C) with trifluoromethylsulfonic acid 2,2,2-trifluoroethyl ester or allyl bromide respectively as described by Bender et al., J. Med. Chem., 28, 1169 (1985), for preparation of compounds No. 23 and 33 described therein. Appropriately substituted mono and dihydroxy phenyl compounds or disubstitued phenyl compounds wherein one substituent is hydroxy of Formula (C) and Formula (II) are obtained by treatment of their respective correspondingly substituted methoxy derivatives with HBr in acetic acid, or preferably with BBr_3 in CH_2Cl_2 by the method described by Bender et al., J. Med. Chem., 28, 1169 (1985), for the preparation of compound No. 14 described therein.

Compounds of Formula (II) or Formula (C) where R is C_{1-3}alkoxy mono- or di- substituted phenyl are prepared by alkylation of the appropriately substituted hydroxyphenyl compounds with the corresponding C_{1-3} alkylhalide in the presence of a strong base such as sodium hydride in an aprotic organic solvent such as dimethylformamide.

Compounds of Formula (II) wherein R or R^1 is phenyl di-substituted with an acyloxyalkylthio group wherein the alkyl is optionally substituted with C_{1-4}alkyl are prepared by treating a compound of Formula (IIa) wherein R^1 is phenyl substituted with at least one alkylsulfinyl group with an alkanoic acid anhydride. Hydrolysis of the resulting acyloxyalkylthio compounds yields compounds of Formula (G) wherein one of R^1 or R is phenyl substituted with a sulfhydryl function. The sulfhydryl substituted compounds can be treated with an alkanoic acid anhydride or an alkylthiono acid chloride in pyridine or a hindered amine, such as di(C_{1-3}alkyl)amine under appropriate conditions, to prepare compounds of Formula (G) wherein one of R^1 or R is phenyl substituted with one or more acylthio or dithioacyl groups.

Compounds of Formula (II) wherein one of R^1 or R is phenyl substituted with at least one thiocarbamyl or dithiocarbamyl group are prepared by treating the sulfhydryl-containing Formula (G) compound, prepared as above,with a carbamyl halide or thiocarbamyl halide in the presence of a base such as pyridine to yield the desired compounds. The two hydrogen atoms on the respective nitrogen atom in the carbamyl halides or thiocarbamyl halide derivatives may be replaced independently by alkyl, alkenyl, alkynyl, aryl or heteroaryl derivative, which may in turn be optionally substituted.

Compounds of Formula (II) wherein R^1 or R is phenyl disubstituted with an alkenylthio group wherein one saturated carbon atom separates the sulfur from the carbon bearing the double bond can be prepared by alkylating a compound of Formula (G) (or Formula (C) wherein one of R_1 or R_0 may be a phenyl substituted with at least one sulfhydryl group),with an appropriately substituted alkenylhalide, such as allylbromide.

Compounds of Formula (II) or Formula (C), wherein R^1 or R is phenyl substituted with an alkylcarbonylalkylthio or carbalkoxyalkylthio group are prepared by treatment of the corresponding sulfhydryl substituted compounds with an alkylcarbonylalkylhalide, such as bromoacetone, or with a carbalkoxyalkylhalide, such as ethylbromoacetate.

Compounds of Formula (II) wherein R_0 or R_1 is phenyl substituted with an alkenylthio group wherein the sulfur is attached to the carbon bearing the double bond are prepared from the corresponding compounds of Formula (G) or (C), as defined above, wherein the phenyl is substituted with a mercapto group. The mercapto substituted compound is converted to a metal salt in a polar solvent with a strong base such as a metal hydride, a metal alkoxide or lithium diethylamide. The metal mercaptide salt is treated with trialkylsilylmethylchloride in an aprotic solvent such as tetrahydrofuran is treated at reduced temperature with a lithiating reagent such as lithium diethylamide followed by treatment with an appropriate aliphatic aldehyde or ketone to prepare the compounds of Formula (II) and Formula (C),wherein R , R_1 or X, is phenyl substituted with one or more alkenylthio groups.

Compounds of Formula (II) wherein R or R^1 is phenyl substituted with an alkoxycarbonylthio are prepared by reacting a metal mercaptide salt prepared as described above, with an appropriate alkyl or aryl chloroformate. The metal mercaptide salt is formed from a compound of Formula (G) wherein one of R or R^1 is phenyl substituted with a sulfhydryl function prepared as previously described. Compounds of Formula (II) wherein R or R^1 is phenyl substituted with one or more alkoxythionothio groups are prepared by reacting the metal mercaptide with the appropriate alkyl or aryl halothionoformate.

Compounds of Formula (II) wherein R or R^1 is alkoxyalkylthio are prepared by reacting the metal mercaptide salt of Formula (G) or Formula (C), prepared as described above, with an appropriate halomethyl ether. Oxidation of the resulting alkoxyalkylthio compounds by reacting with a suitable oxidizing agent such as chloroperbenzoic acid yields the compounds of Formula (II) wherein R or R^1 is phenyl substituted with an alkoxyalkylsulfinyl.

Compounds of Formula (II) wherein R or R^1 is phenyl substituted with a substituted disulfide group are prepared by mild air oxidation of the compounds of Formula (II) wherein R or R^1 is phenyl substituted with a sulfhydryl group, prepared as described

above. The nonsymmetrical disulfide (Z) wherein Z is -S-S-Z_1 and Z_1 is phenyl or C_{1-9} alkyl, the compound may be prepared by reaction of the sulfhydryl compound with the appropriate sulfenyl halide in an ethereal solvent to afford compounds of Formula (II) wherein one of R or R^1 is phenyl substituted with one or more alkyl-dithio or aryl-dithio groups The method of Mukaiyama et al., Tetrahedron Letters, 56:5907-08 (1968) allows for use of the desired aryl-SH or alkyl-SH reagent treated with diethylazodicarboxylate in 1:1 equivalence at room tempertaure in a solvent, yielding an adduct which is then treated with 1:1 ratio of the desired mercaptan of Formula (G). This process will also yield the disulfide dimer of the compounds of Formula (II). Preferably the disulfide linkage is on the R_0 position of the compounds of Formulas (I) and (II).

Compounds of Formula (II) and Formula (C), wherein R, R_1 or X, is phenyl substituted with an alkylthioalkylthio group are prepared by reacting the analogous sulfhydryl compound, prepared as described above, with the appropriate carbonyl component, such as formaldehyde, acetone, or acetaldehyde, using either mineral or Lewis acid catalysis conditions to yield the symmetrical dithioketal. The intermediate hydroxylalkylthio derivative reacts with another sulhydryl containing compound under the acid catalysis conditions to yield what is essentially a "bis" type compound, differing only by the alkyl chain insertion, i.e. [Formula (II)-S-CRR^1-S-Formula (II)]. The substitution of the alkyl, R,or R^1, is determined by the reactive carbonyl functional group, wherein R or R^1 may be C_{1-9} alkyl, aryl or heteroaryl, all optionally substituted. The nonsymmetrical thioketals can be prepared by the reaction of the metal mercaptan salt, prepared as described above, with a halomethyl thioether to yield compounds of Formula (II) wherein one of R or R_1 is phenyl substituted with one or more alkylthioalkylthio groups. The metal salt reacts with an independent and varying alkyl chain length halomethyl-[CRR^1]-thioalkyl[aryl/heteroaryl] compound to yield the "non-bis" type compounds, [Formula (I)-S-CRR^1-S-R^2], wherein R and R^1 are as defined above for the "bis" compounds, and R^2 is a C_{1-9} alkyl, aryl or heteroaryl group which may be optionally substituted. A mixture of R_0 and R_1 linkages is contemplated, as part of the present invention, hoever, preferably the linkage is on both R_0 positions of the compounds of Formula (I) or (II).

An alternate method of preparation of the nonsymmetrical disulfide compound, wherein only one component is a compound of Formula (II), and the other half of the disulfide link is an alkyl, aryl or heteroaryl derivative, may be prepared by reaction of a sulfhydryl compound of Formula (II), with the appropriate sulfenyl halide, in an ethereal solvent to afford compounds of Formula (II) wherein one of R or R^1 is phenyl substituted with one or more [alkyl]- dithio groups, i.e. [Formula (II)-S-S-R^2], wherein R-R_2 are as defined in the above paragraph. The contemplated sulfenyl halide derivatives of alkyl, aryl, or heteroaryl groups may be optionally substituted.

The disulfide compound(s) may also be prepared from the corresponding alkyl sulfoxide compounds, such as methylsulfinyl, propylsulfinyl, iso-propylsulfinyl, wherein the alkyl can be a straight chain or branched derivative having from 1 to 9 carbon atoms, in a solvent, preferably a chlorinated one such as chloroethylene, methylene chloride or chloroform, to which is added a carboxcylic acid anhydride, such as trifluroacetic anhydride, or acetic anhydride. The Pummerer rearrangement reaction may require some heating prior to addition of an alkali metal hydroxide, such as sodium hydroxide. If acetic anhydride is used than heating is also likely to be needed during the hydroxide treatment, before addition of iodine solid (I_2), which then affords the symmetrical disulfide compound as is noted above Mixtures of the sulfoxide compounds may be present in the solution to yield "symmetrical" compounds but with varying substituent groups on the di-heteroaryl-imidazole ring system of the present invention.

This invention also relates to the use of a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (IA) and a pharmaceutically acceptable carrier or diluent in the methods disclosed herein.

Pharmaceutically acceptable salts and their preparation are well known to those skilled in pharmaceuticals. Pharmaceutically acceptable salts of the compounds of Formula (I) which are useful in the present invention include, but are not limited to, maleate, fumarate, lactate, oxalate, methanesulfonate, ethane-sulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate and phosphate salts. Preferred pharmaceutically acceptable salts of the compounds of Formula (I) include hydrochloride and hydro-bromide salts, and such salts can be prepared by known techniques such as the method of Bender et al., U.S. Patent 4,175,127, the disclosure of which is hereby incorporated by reference.

METHOD OF TREATMENT

It has now been discovered that the compounds of Formula (I) are useful for treating disease states mediated by the 5-lipoxygenase pathway of arachidonic acid metabolism in an animal, including mammals, in need thereof. The discovery that the compounds of Formula (I) are inhibitors of the 5-lipoxygenase pathway is based on the effects of the compounds of Formula (I) on the production of 5-lipoxygenase products in blood ex vivo and on the 5-lipoxygenase in vitro assays, some of which are described hereinafter. The 5-lipoxygenase pathway inhibitory action of the compounds of Formula (I) was confirmed by showing that they impaired the production of 5-lipoxygenase products such as leukotriene B_4 production by RBL-1 cell supernants.

The pathophysiological role of arachidonic acid metabolites has been the focus of recent intensive studies. In addition to the well-described phlogistic activity (i.e. general inflammatory activity) of prostaglandins, the more recent description of similar

activity for eicosanoids has broadened the interest in these products as mediators of inflammation [See, O'Flaherty, Lab. Invest., 47, 314-329 (1982)]. The reported discovery of potent chemotactic and algesic activity for LTB_4 [see, Smith, Gen. Pharmacol., 12, 211-216 (1981) and Levine et al., Science, 225, 743-745 (1984)], together with known LTC_4 and LTD_4-mediated increase in capillary permeability [see, Simmons et al., Biochem. Pharmacol., 32, 1353-1359 (1983), Vane et al., Prostaglandins, 21, 637-647 (1981), and Camp et al., Br. J. Pharmacol., 80, 497-502 (1983)], has led to their consideration as targets for pharmacological intervention in both the fluid and cellular phases of inflammatory diseases.

The pharmacology of several inflammatory model systems has attested to the effectiveness of corticosteroids in reducing the cellular infiltration. These results, and the observation that corticosteroids inhibit the generation of both cyclooxygenase and lipoxygenase products, suggest that such dual inhibitors may effectively reduce both the fluid and cellular phases of the inflammatory response since selective cyclooxygenase inhibitors do not reliably inhibit cell influx into inflammatory sites [See, Vinegar et al., Fed. Proc., 35, 2447-2456 (1976), Higgs et al., Brit. Bull., 39, 265-270 (1983), and Higgs et al., Prostaglandins, Leukotrienes and Medicine, 13, 89-92 (1984)]. Under optimal conditions, it is likely that an agent with preferential lipoxygenase inhibitory activity would not share the ulcerogenic liability of cyclooxygenase inhibitors or the toxicity of corticosteroids. This may suggest that the compounds of the present invention could be useful in treating diseases where it is beneficial to limit ulcerogenic activity or steroidal side effects such as osteoarthritis. [See Palmoski et al., "Benoxaprofen Stimulates Proteoglycan Synthesis in Normal Canine Knee Cartiledge in Vitro," Arthritis and Rheumatism 26, 771-774 (1983) and Rainsford, K.D., Agents and Actions 21, 316-319 (1987).]

Clinical data supports the enthusiasm for inhibitors of the 5-lipoxygenase pathway in a variety of inflammatory diseases in which granulocyte and/or monocyte infiltration is prominent. The reported demonstration of elevated levels of LTB_4 in rheumatoid arthritic joint fluid [See, Davidson et al., Ann. Rheum. Dis., 42, 677-679 (1983)] also suggests a contributing role for arachidonic acid metabolites in rheumatoid arthritis. Sulfasalazine, which is used for treatment of ulcerative colitis, has been reported to inhibit LTB_4 and 5-HETE production in vitro [See, Stenson et al., J. Clin. Invest., 69, 494-497 (1982)]. The recently reported preliminary observation of efficacy, including remission, reported with sulfasalazine treatment of rheumatoid arthritic patients [See Neumann et al., Brit. Med. J., 287, 1099-1102 (1983)] illustrates the utility of inhibitors of the 5-lipoxygenase pathway in rheumatoid arthritis.

Additionally it has been reported that inflamed gastrointestinal mucosa from inflammatory bowel disease patients showed increased production of LTB_4 [See, Sharon et

al., Gastroenterol., 84, 1306 (1983)], which suggests that sulfasalazine can be effective by virtue of inhibition of production of chemotactic eicosanoids (such as the 5-lipoxygenase pathway product known as LTB_4). The observations serve to underscore utility of inhibitors of the 5-lipoxygenase pathway in inflammatory bowel disease.

Another area of utility for an inhibitor of the 5-lipoxygenase pathway is in the treatment of psoriasis. It was demonstrated that involved psoriatic skin had elevated levels of LTB_4 [See, Brain et al., Lancet, 19, February 19, 1983]. The promising effect of benoxaprofen on psoriasis [See, Allen et al., Brit. J. Dermatol., 109, 126-129 (1983)], a compound with in vitro lipoxygenase inhibitory activity lends support to the concept that inhibitors of the 5-lipoxygenase pathway can be useful in the treatment of psoriasis.

Lipoxygenase products have been identified in exudate fluids from gouty patients. This disorder is characterized by massive neutrophil infiltration during the acute inflammatory phases of the disease. Since a major 5-lipoxygenase product, LTB_4, is produced by neutrophils, it follows that inhibition of the synthesis of LTB_4 may block an amplification mechanism in gout.

Another area in which inhibitors of the 5-lipoxygenase product can have utility is in myocardial infarction. Studies in dogs with the dual inhibitor, BW755-C, demonstrated that the area of infarction following coronary occlusion was reduced, and such reduction was attributed to inhibition of leukocyte infiltration into the ischaemic tissue [See, Mullane et al., J. Pharmacol. Exp. Therap., 228, 510-522 (1984)].

Yet another area of utility for inhibitors of the 5-lipoxygenase pathway is in the area of prevention of rejection of organ transplants. [See, e.g., Foegh et al., Adv. Prostaglandin, Thromboxane, and Leukotriene Research, 13, 209-217 (1983).]

Yet another utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of tissue trauma. [See, e.g., Denzlinger et al. Science, 230 (4723), 330-332 (1985)].

Furthermore, another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of inflammatory reaction in the central nervous system, including multiple sclerosis. [See, e.g., Mackay et al., Clin. Exp. Immunology, 15, 471-482 (1973)].

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of asthma. [See, e.g., Ford-Hutchinson, J. Allergy Clin. Immunol., 74, 437-440 (1984)]. Additionally another utility for inhibitors of the 5-lipoxygense pathway is in the treatment of Adult Respitory Distress Syndrome. [See, e.g., Pacitti et. al., Circ. Shock , 21, 155-168 (1987)]. Yet another utility for inhibitors of the 5-lipoxygenase pathway is in the treament of allergic rhinitis.

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of vasculitis, glomerulonephritis, and immune complex disease. [See Kadison et

al., "Vasculitis: Mechanism of Vessel Damage" in Inflammation: Basic Principles and Clinical Correlates, 703-718, Ed. Gallin et al., Raven Press, N.Y., N.Y. (1988).]

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of dermatitis. [See Pye et al., "Systemic Therapy" in Textbook of Dermatology, Vol. III, 2501-2528, Ed. Rook et al., Blackwell Scientific Publications, Oxford, England (1986).]

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of atherosclerosis. Recent studies have shown that inhibition of oxidative modification of low density lipoprotein slows progression of atherosclerosis, and that inhibitors of lipoxygenase effectively inhibit cell-induced oxidative modification. [See Carew et al., Proc. Natl. Acad. Sci. USA, 84, 7725-7729, November 1987; and Steinberg, D., Cholesterol and Cardiovascular Disease, 76, 3, 508-514 (1987).]

An additional area of utility for inhibitors of the 5-lipoxygenase pathway is in the optical area, in particular general inflammation of the corneal anterior and posterior segments due to disease or surgery such as in post surgical inflammation, uveitis, and allergic conjuntivitis. [See Rao N. et al. Arch. Ophathmal. 105 (3) 413-419 (1987); Chiou, L. and Chiou, G. J. Ocular Pharmacol. 1, 383-390 (1985); Bazan H., J. Ocular Pharma. 4, 43-49 (1988); and Verbey N.L. et al., Current Eye Research 7, 361-368 (1988).]

Yet another area in which inhibitors of lipid peroxidation involved in the OPUFA mediated can have utility is that generally refered as degenerative neurological disorders, such as Parkinson's disease. Another area is that of traumatic or ischemic injuries, such as stroke, brain or spinal cord injuries and inflammatory disease of the brain and spinal column. More specicially preferred disease states are the mycardial induced ischemic injuries and/or reperfusion injuries. [See, Braughler et al., Jour. Biol. Chem., Vol. 262, No. 22, pp10438-40 (1987), see also Xu et al., J. Neurochemistry, 55, 907-912 (1990); Asano et al., Molecular and Chemical Neuropathology, 10:101-133 (1989) and Bracken et al., NE. J. Med., 322:1405-1411 (1990)]

It has also been discovered that the compounds of Formula (I) are useful for treating disease states mediated by the cyclooxygenase pathway of arachodonic acid in an animal, including mammals, in need thereof. The discovery that the compound of Formula (I) are inhibitors of cyclooxygenase products is based upon the effects of the compounds of Formula (I) on the production of the PGE_2 products, and the human monocyte data, the assays of which are described herein.

FORMULATION OF PHARMACEUTICAL COMPOSITIONS

This invention also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a Formula (I), Formula (II) or (III) compound or salt thereof, and a pharmaceutically acceptable carrier or diluent for use in the methods described herein. The compounds of Formula (I), Formula (II) or (III) are administered in conventional dosage forms prepared by combining a compound of Formula (I), Formula (II) or (III) in an amount sufficient to produce an OPUFA inhibiting, 5-LO inhibiting or CO inhibiting activity with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I), Formula (II), or Formulas (III) may also be administed in conventional dosages in combination with a known, second therapeutically active compound, such as an antihistamine, anti-bacterial or anti-fungal agent. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

This invention relates to a pharmaceutical composition comprising an effective amount of a compoundor a pharmaceutically acceptable salt thereof of 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo[1,2-a]imidazole; 5,6-Dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]imidazole-7-ol; or 5,6-Dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]-imidazole and a pharmaceutically acceptable carrier or diluent for treating an OPUFA, specifically a 5-LO, or CO pathway mediated disease state. These compounds are administered in conventional doseage forms prepared by combining them in an amount sufficient to produce OPUFA, 5-LO inhibiting or CO inhibiting activity with standard pharmaceutical carriers according to conventional procedures.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

To obtain a stable water soluble dose form of an insoluble Formula (I) or Formula (II) compound, a pharmaceutically acceptable salt of the Formula (I) or Formula (II) compound is dissolved in an aqueous solution of an organic or inorganic acid, such as a 0.3 M solution of succinic acid or, preferably, citric acid.

Preferably, each parenteral dosage unit will contain the active ingredient [i.e., the compound of Formula (I) or (II)] in an amount of from about 50 mg. to about 500 mg. Preferably, each oral dosage will contain the active ingredient in an amount of from about 100 mg to about 1000 mg.

The compounds of Formula (I) or (II) may also be administered topically. Thus, the compounds of Formula (I) or Formula (II) may be administered topically in the treatment or prophylaxis of inflammation in an animal, including man and other mammals,and may be used in the relief or prophylaxis of 5-lipoxygenase pathway mediated diseases such as rheumatoid arthritis, rheumatoid spondylitis,osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The amount of a compound of Formula (I) or Formula (II) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the inflammatory condition and the animal undergoing treatment, and is ultimately at the discretion of the physician. A suitable anti-inflammatory dose of an active ingredient is 1.5 mg to 500 mg of base for topical administration, the most preferred dosage being 1 mg to 1000 mg, for example 5 to 250 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) or (II) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention ,both for veterinary and human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as

liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as prolylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic sulfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The compounds of Formula (I) or (II) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of a compound of Formula (I) or (II) administered by inhalation is from about .1mg to about 100 mg/kg preferably about 1 mg to about 10 mg/kg per day.

A compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof can be administered to such human in a conventional dosage form prepared by combining a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, with a conventional pharmaceutically acceptable carrier or diluent according to known techniques, such as those described above as well as those described in Adams et al., U.S. Patent Number 5,002,942, issued March 26, 1991. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables.

The route of administration may be oral, pulmonary, parenteral, buccal, intra-articular ,nasal or topical. The term parenteral as used herein includes intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily oral dosage regimen will preferably be from about 5 to about 100 mg/kilogram of total body weight. The daily parenteral dosage regimen will preferably be from about 2 to about 80 mg per kilogram (kg) of total body weight, most preferably from about 3 to about 60 mg/kg. The daily topical dosage regimen will preferably be from about 2 mg to about 10 mg per site of administration. It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or (II) or pharmaceutically acceptable salts thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques.

It will also be appreciated by one of skill in the art that the optimal quantity and spacing of individual dosages of the Formula (I) or (II) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular animal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatmen: determination tests.

The route of administration for the compounds an their pharmaceutically acceptable salts of 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo[1,2-a]imidazole; 5,6-Dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]imidazole-7-ol; or 5,6-Dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]-imidazole may be by oral, pulmonary, parenteral, buccal, intra-articular ,nasal or topical means as defined herein. The subcutaneous and

intramuscular forms of parenteral administration are generally preferred. The daily oral dosage regimen will preferably be from about 1 to about 100 mg/kilogram of total body weight dependent upon the route of administration, preferably from about 2mg to about 80mg/kg per day. It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of one of these three compounds or pharmaceutically acceptable salts thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

PHARMACEUTICAL COMPOSTION EXAMPLES

EXAMPLE A - CAPSULE COMPOSITION

A pharmaceutical composition of this invention in the form of a capsule is prepared by filling a standard two-piece hard gelatin capsule with 50 mg. of a compound of Formula (I), in powdered form, 110 mg. of lactose, 32 mg. of talc and 8 mg. of magnesium stearate.

EXAMPLE B - INJECTABLE PARENTERAL COMPOSITION

A pharmaceutical composition of this invention in a form suitable for administration by injection is prepared by stirring 1.5% by weight of a compound of Formula (I) in 10% by volume propylene glycol and water. The solution is sterilized by filtration.

EXAMPLE C - OINTMENT COMPOSITION

Compound of Formula (I) 1.0 g
White soft paraffin to 100.0 g

The compound of Formula (I) is dispersed in a small volume of the vehicle and this dispersion is gradually incorporated into the bulk to produce a smooth, homogeneous product which is filled into collapsible metal tubes.

EXAMPLE D - TOPICAL CREAM COMPOSITION

Compound of Formula (I) 1.0 g
Carbowax 200 20.0 g
Lanolin Anhydrous 2.0 g
White Beeswax 2.5 g
Methyl hydroxybenzoate 0.1 g
Distilled Water to 100.0 g

The carbowax, beeswax and lanolin are heated together at 60°C and added to a solution of methyl hydroxybenzoate. Homogenization is achieved using high speed stirring and the temperature is allowed to fall to 50°C. The compound of Formula (I) is added and dispersed throughout, and the composition is allowed to cool with slow speed stirring.

EXAMPLE E - TOPICAL LOTION COMPOSITION

Compound of Formula (I) 1.0 g
Sorbitan Monolaurate 0.6 g
Polysorbate 20 0.6 g
Cetostearyl Alcohol 1.2 g
Glycerin 6.0 g
Methyl Hydroxybenzoate 0.2 g
Purified Water B.P. to 100.00 ml

The methyl hydroxybenzoate and glycerin are dissolved in 70 ml of the water at 75°C. The sorbitan monolaurate, polysorbate 20 and cetostearyl alcohol are melted together at 75°C and added to the aqueous solution. The resulting emulsion is homogenized, allowed to cool with continuous stirring and the compound of Formula (I) is added as a suspension in the remaining water. The whole suspension is stirred until homogenized.

EXAMPLE F - EYE DROP COMPOSITION

Compound of Formula (I) 0.5 g
Methyl Hydroxybenzoate 0.01 g
Propyl Hydroxybenzoate 0.04 g
Purified Water B.P. to 100.00 ml

The methyl and propyl hydroxybenzoates are dissolved in 70 ml purified water at 75°C and the resulting solution is allowed to cool. The compound of Formula (I) is then added, and the solution is made up to 100 ml with purified water. The solution is sterilized by filtration through a membrane filter (0.22 mm pore size) and packed aseptically into suitable sterile containers.

EXAMPLE G - COMPOSITION FOR ADMINISTRATION BY INHALATION

For an aerosol container with a capacity of 15-20 ml: Mix 10 mg of a compound of Formula (I) with 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such mixture in a propellant (c.a.), such as freon, preferably a combination of freon 114 and freon 12, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

EXAMPLE H - COMPOSITION FOR ADMINISTRATION BY INHALATION

For an aerosol container with a capacity of 15-20 ml: Dissolve 10 mg of a compound of Formula (I) in ethanol (6-8 ml), add 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such in a propellant (c.a.), such as freon, preferably a combintion of freon 144 and freon 12, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

UTILITY EXAMPLES

In the tests used to determine activity as 5-lipoxygenase pathway inhibitors, male Balb/c mice (20-28 g), were used. All mice were obtained from Charles River Breeding Laboratories, Kingston, N.Y. Within a single experiment, mice were age matched.

Reagents were employed as follows:

Compounds of Formula (I) were used as the free base. The compounds were dissolved in acid saline. Compounds were administered by lavage at the indicated dose in a final volume of 10 ml/kg.

For in vitro experiments, compounds were dissolved at appropriate concentrations in ethanol (final concentration 1.0%) and then diluted to final concentrations using the buffers indicated in the text.

Arachidonic Acid-Induced Mouse Ear Inflammation

Arachidonic acid in acetone (2 mg/20 ml) was applied to the inner surface of the left ear. The thickness of both ears was then measured with a dial micrometer one hour after treatment, and the data were expressed as the change in thickness (10^{-3} cm) between treated and untreated ears.

Test compounds were given orally in acid/saline at the times indicated in the text prior to the topical application of arachidonic acid.

Assay of 5-Lipoxygenase Activities

The 5-lipoxygenase (5-LO) was isolated from extracts of RBL-1 cells. These cells were obtained from the American Type Culture Collection (#CRL 1378) and were grown at 37° with 5% CO_2 in spinner culture using Eagles essential medium (MEM) supplemented medium with 10% heat inactivated fetal calf serum. The cells were collected

from culture by centrifugation at 2,000xg for 20 minutes and then washed twice with 50mM sodium phosphate (pH 7.0) that contained lmM EDTA and 0.1% gelatin. After this wash, the cells were resuspended in fresh phosphate buffer to achieve a concentration of $5X10^7$ cells/ml. This suspension was disrupted by nitrogen cavitation using the Parr bomb at 750psi for 10 minutes. The broken cells were then centrifuged at 10,000xg for 20 minutes. The supernatant was collected and centrifuged at 100,000 xg for 60 minutes. This supernatant was collected and stored at -70°C until assayed.

The inhibition of 5-lipoxygenase activity was measured by one of two assays, the radiotracer extent assay either measured after 90 seconds at 20°C or measured according to the method of G. K. Hogaboom et al., Molecular Pharmacol. 30, 510-519 (1986) or the continuous O_2 consumption assay. The results from either assay are comparable if not identical. All compounds were dissolved in ethanol with the final concentration of ethanol being 1% in the assay.

The radiotracer extent assay examined the 5-lipoxygenase products [transLTB$_4$ (DI-HETE), 5HETE and 5HPETE] produced after a 90 second incubation at 20°C. Aliquots (40mL) of the supernatant were preincubated with the inhibitor or vehicle for 10 minutes in 25mM BisTris buffer (pH 7.0) that also contained 1mM EDTA. 1mM ATP, 50mM NaCl, 5% ethylene gylcol and 100 mg/ml of sonicated phosphatidylcholine (total volume 0.238 ml). The 5-lipoxygenase reaction was initiated by the addition of $CaCl_2$ (2mM) and 1-C14-arachidonic acid (25mM; 100,000dpm))(final volume 0.25ml). After 90 seconds, the reaction was terminated by the addition of two volumes (0.5ml) of ice chilled acetone. The sample was allowed to deproteinize on ice for 10 minutes prior to centrifuging at 1,000 xg for 10 minutes. The deproteinized supernatants were dried under argon and then redissolved in 200 mL of ethanol. These samples were then analyzed by reverse phase HPLC as described by G.K. Hogaboom et al., Molecular Pharmacol. 30: 510-519 (1986), herein incorporated by reference. The compound-mediated inhibition of 5-lipoxygenase activity is described as the concentration of compound causing a 50% inhibition of product synthesis.

The second assay for assessing inhibition of the 5-lipoxygenase activity was a continuous assay which monitored the consumption of 0_2 as the reaction progressed. The 5-lipoxygenase enzyme (200mL) was preincubated with the inhibitor or its vehicle in 25mM BisTris buffer (pH 7.0) that contained 1mM EDTA, 1mM ATP, 5mM NaCl and 5% ethylene glycol for 2 minutes at 20°C (total volume 2.99 ml). Arachidonic acid (10mM) and $CaCl_2$ (2mM) were added to start the reaction, and the decrease in 0_2 concentration followed with time using a Clark-type electrode and the Yellow Spring 0_2 monitor (type 53)(Yellow Springs, OH). The optimum velocity was calculated from the progress curves. The compound mediated inhibition of 5-lipoxygenase activity is described as the

concentration of compound causing a 50% inhibition of optimum velocity for the vehicle-treated sample.

LTC-4 / PGE_2 Production from Human Monocytes in vitro

a) Cell Preparation: Human monocytes were prepared from leukosource packs supplied by the American Red Cross (Philadelphia,Pa). The leukosource packs were fractionated by a two-step procedure described by F. Colatta et al., J. Immunol. 132, 936 (1984), herein incorporated by reference, that uses sequential sedimentation on Ficoll followed by sedimentation on Percoll. The monocyte fraction that results from this technique was composed of greater than 85% monocytes (with the remainder being neutrophils and lymphocytes). The monocytes (1.5×10^6) were placed into polypropylene tubes and used as a suspended culture. The assay buffer consisted of RPMI 1640 buffer, [Moore, G. E. et al., JAMA, 199, 519 (1967) herein incorporated by reference] 1% human AB serum, 2mM glutamine, 100 U/ml Penicillin/Streptomycin, 25 mM HEPES [4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid], and 1mM $CaCl_2$.

b) LTC4/PGE2 Production: Monocytes (0.9ml/tube) were dispensed into 12 X 75 mm polypropylene tubes (as a suspended culture). Compounds (100ul of a 10X stock of the compound of interest) dissolved in the assay media was added per tube (performed in duplicte). The cells were incubated for about 45 minutes at about 7°C with constant agitation in a humidified incubator. A23187 calcium ionophore (2uM final concentration) used to stimulate the cells, was added and the monocytes were incubated an additional 15 minutes. Supernatants were then collected from each tube, clarified by centrifugation, divided into two aliquots and stored at -70°C until assayed.

c) Radio-immunoassay: Supernatants were assayed for LTC_4 production and PGE_2 by radioimmunassay; which was performed using a New England Nuclear Leukotriene [^{3}H]-LTC_4 and [^{125}I]-PGE_2 RIA Kit according to the manufacturer's (New England Nucelar, Boston Massachusetts) instructions. The compound-mediated inhibition of LTC_4 is described as the concentration of compound causing a 50% inhibition of LTC_4 production.

TABLE 1

ANTIINFLAMMATORY ACTIVITY OF FORMULA (I)

PERCENT INHIBITION OFARACHIDONIC ACID-INDUCEDMOUSE EAR SWELLING[a] (50 mg/kg p.o.)

COMPOUND NUMBER[b] .....1.....65.0

[a] Mouse ear edema was measured as described in Griswold et al., Inflammation, 11(2), 189-199 (1987), the disclosure of which is hereby incorporated by reference.

[b] compound no. 1 is 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine.

TABLE II - 5-LO DATA :

COMPOUND NUMBER[b] .....1 .....16.0
COMPOUND NUMBER[c] .....2.....36.0
COMPOUND NUMBER[d] .....3.....greater than 100
COMPOUND NUMBER[e] .....4.....greater than 100

[c] compound no. 2 is 5,6-Dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]-imidazole.

[d] compound no. 3 is 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo[1,2-a]imidazole.

[e] compound no. 4 is 5,6-Dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]imidazole-7-ol.

TABLE III - LTC_4 DATA:

COMPOUND NUMBER[b] .....1.....12.0.
COMPOUND NUMBER[c] .....2.....15.0
COMPOUND NUMBER[d] .....3.....33.0
COMPOUND NUMBER[e] .....4.....18.0

TABLE IV - PGE_2 DATA

COMPOUND NUMBER [b] .....1.....0.4

RESULTS

Based upon the data shown herein the compounds of Formula (I) show inhibition of both 5-LO and CO activity and the 7-substituted difluroro, 7-oxo and 7-hydroxy derivatives of a pyrrolo[2,1-a]imidazole, and therefore are expected to be useful in the treatment of OPUFA , specifically mediated by inhibition of the 5-LO and CO mediated enzymes.

SYNTHETIC EXAMPLES

EXAMPLE 1

2-(4-Mercaptophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

Formula (G) Compound

The title compound is prepared by treating 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyridine, prepared as described in Example 15, of Bender et al., U.S. Aplication Serial Number 07/365,349, filed June 13, 1989.

A solution of 5.17 g (15.5 mmoles) of 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine in methylene chloride is cooled to 0°C is treated with 9.7 g (46.4 mmoles, 6.5 ml) of trifluoroacetic anhydride in methylene chloride. The mixture is heated to reflux for 1 hour and stripped in vacuo. The residue is treated with water and extracted into methylene chloride. The organic phase is washed with aqueous sodium bicarbonate, saturated brine, dried over anhydrous sodium sulfate and stripped in vacuo. A solution of this residue in anhydrous methanol is neutralized with 5 ml (23 mmoles) of a 25% solution of sodium methoxide in methanol and stirred at room temperature for 3 hours. This solution is then poured into ice-water, treated with 3N sodium bicarbonate solution, and concentrated in vacuo to remove most of the methanol. This mixture is then extracted into methylene chloride, and the organic phase is washed with water, saturated brine, dried over anhydrous sodium sulfate and stripped in vacuo. The residue is chromatographed on silica to afford the title compound.

EXAMPLE 2

2-(4-Ethoxycarbonylthiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

To an ice-bath cooled solution containing 1.03 g, (3.4mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, and 0.5ml (3.6mmole) of triethylamine in 10ml of methylene chloride is added 0.33ml (3.5mmole) of ethyl chloroformate. The reaction is allowed to warm to room temperature and stirred for several hours. The mixture is then diluted with methylene chloride and washed with 3N $NaHCO_3$, saturated NaCl, treated with Na_2SO_4, stripped, then flash

chromatographed on silica with methylene chloride containing MeOH to give the desired titled compound.

EXAMPLE 3

2-(4-Phenoxythiocarbonylthiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

To an ice-bath cooled solution containing 1.03 g (3.4mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, and 0.5 ml (3.6 mmole) of triethylamine in 10 ml of diglyme is added 0.48 ml (3.5mmole) of phenyl chlorothionoformate. The reaction is allowed to warm to room temperature and heated at 40° to 120°C for several hours. Workup and chromatography in a manner analogous to that outlined in Example 2 affords the desired titled compound.

EXAMPLE 4

2[4-(2-Oxobutyl)thiophenyl]-3-(4-pyridyl)-imidazo[1,2-a]pyridine

To an ice-bath cooled solution containing 1.0 3g (3.4mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, and 0.5 ml (3.6 mmole) of triethylamine in 10 ml of methylene chloride is added 0.36 ml (3.5mmole) of 1-bromo-2-butanone. The reaction is allowed to warm to room temperature and stirred at room temperature for several hours. Workup and chromatography in a manner analogous to that outlined in Example 2 affords the desired titled compound.

EXAMPLE 5

2-(4-Methoxymethylthiophenyl]-3-(4-pyridyl)-imidazo[1,2-a]pyridine

To an ice-bath cooled solution containing 1.03 g (3.4mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, and 0.5 ml (3.6 mmole) of triethylamine in 10ml of methylene chloride is added 0.27 ml (3.5 mmole) of bromomethyl methyl ether. The reaction is allowed to warm to room temperature and stirred at room temperature for several hours. Workup and chromatography in a manner analogous to that outlined in Example 2 affords the desired titled compound.

EXAMPLE 6

2,2-Propan-diyl-bis[2-(4-thiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

To an ice-bath cooled solution containing 1.03 g (3.4 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 and 0.12 ml (1.7 mmole) of acetone in 5 ml of methylene chloride is added 0.10 ml of boron trifluoride etherate. After 4 hours at 0°C the reaction is diluted with methylene chloride and

worked up as outlined in Example 2. Purification by chromatography on silica affords the desired dithioketal.

EXAMPLE 7

2-(4-Mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine disulfide

2.06g. (6.8 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, is dissolved in a solution containing 4 parts ethanol and 1 part concentrated aqueous ammonia and allowed to air oxidize in an open flask at 20-40°C for 1 to 4 days. The solvent is stripped in vacuo and the product is purified by chromatography on silica to yield the desired disulfide.

In an alternate procedure to that described in above 2-(4-Mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine is prepared in situ by adding to a stirred, ice-cooled solution containing 1.03g of the sulfoxide, 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine in 7 ml of chloroethylene, 1.27 ml of trifluroacetic anhydride. The solution is allowed to warm and stirred at room temperature for about 2 hours at which point 10ml of ethanol and 3ml of a 10% sodium hydroxide solution is added. Fifteen minutes later I_2 (800mg) is added. After about an additional 1 hour of stirring the reaction mixture is diluted with methylene chloride, washed with a 10% sodium hydroxide solution, and dried over potassium carbonate. Flash chromatography on silica affords the desired title compound.

EXAMPLE 8

2-(4-Ethyldithiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

Ethanesulfenyl chloride (0.33 g) is added dropwise to an ice-bath cooled solution containing 1.03 g (3.4 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, in tetrahydrofuran. The mixture is allowed to warm to room temperature. Workup yields the crude disulfide which is purified by chromatography on silica.

EXAMPLE 9

2-(4-N-Phenylaminocarbonylthiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

Phenyl isocyanate (0.38ml, 3.5mmole) is added dropwise to a stirring ice-bath cooled solution containing 1.03 g (3.4 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, in tetrahydrofuran. The mixture is allowed to warm to room temperature. Workup yields the crude titled compound which is purified by chromatography on silica.

EXAMPLE 10

2-(4-N-Phenyldithiocarbamoylphenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

Phenyl isothiocyanate (0.42 ml, 3.5 mmole) is added dropwise to a stirring ice-bath cooled solution containing 1.03 g (3.4 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example1 in tetrahydrofuran. The mixture is allowed to warm to room temperature and stirred for several hours. Workup yields the crude titled compound which is purified by chromatography on silica.

EXAMPLE 11

2-(4-Dithiocarbamoylphenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

Thiocarbamoyl chloride (336 mg, 3.5mmole) is added dropwise to a stirring ice-bath cooled solution containing 1.03 g (3.4 mmole) of 2-(4-mercaptophenyl)--3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, in tetrahydrofuran. The mixture is allowed to warm to room temperature and stirred for several hours. Workup yields the crude titled compound which is purified by chromatography on silica.

EXAMPLE 12

2-(4-N,N-Dimethylaminocarbonylthiophenyl)--3-(4-pyridyl)-imidazo[1,2-a]pyridine

N,N-Dimethylcarbamoyl chloride (375 mg, 3.5 mmole) is added dropwise to a stirring -20°C solution containing 1.03g (3.4 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above, in tetrahydrofuran. The mixture is allowed to warm to room temperature. Workup yields the crude thiocarbamate which is purified by chromatography on silica.

EXAMPLE 13

2-(4-Dithiobenzoylphenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine

Thiobenzoyl chloride (546 mg, 3.5 mmole) is added dropwise to a stirring ice-bath cooled solution containing 1.03g (3.4 mmole) of 2-(4-mercaptophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine prepared as in Example 1 above in tetrahydrofuran. The mixture is allowed to warm to room temperature and stirred for several hours. Workup yields the crude titled compound which is purified by chromatography on silica.

EXAMPLE 14

6-(4-Methylsulfinylphenyl)-5-(4-pyridyl)imidazo[2,1-b]thiazole.

Formula (I) Compound

The title compound is prepared by treating 6-(4-methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]thiazole, as described in Example 20 of Bender et al., U.S. Application Serial Number 07/365,349, filed June 13, 1989.

EXAMPLE 15

6-(4-Methylsulfinylphenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole.

Formula (I) Compound

The title compound is prepared by treating 6-(4-methylthiophenyl)-5-(4-pyridyl)-imidazo[2,1-b]oxazole,as described in Example 23, Bender et al., U.S. Application Serial Number 07/365,349, filed June 13, 1989.

EXAMPLE 16

2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyrimidine

Formula (I) Compound

The title compound is prepared by treating 2-(4-methylthiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]-pyrimidine, as described in Example 26, Bender et al., U.S. Application Serial Number 07/365,349, filed June 13, 1989.

EXAMPLE 17

2-(4-Methoxyphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine.

Formula (I) Compound

a) 2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine

A chloroform solution of 7.3 g (32 mmoles) of 1-(4-methoxyphenyl)-2-bromo-ethan-1-one and 3.0 g (32 mmoles) of 2-aminopyridine was stirred for 5 hours and a precipitate was obtained on chilling. This precipitate was washed with cold carbon tetrachloride and recrystallized from ethyl acetate to afford the title compound, melting point (mp) 135-137°C, Calcd for $C_{14}H_{12}N_2O$; C: 74.98; H: 5.39, N: 12.49, Found, C: 74.64, H: 5.35, N: 12.63.

b) 2-(4-Methoxyphenyl)-3-(1-ethoxycarbonyl-1,4-dihydropyridyl)imidazo[1,2-a]pyridine

A solution of 1.5 g (6.69 mmoles) of 2-(4-methoxyphenyl)imidazo[1,2-a]pyridine, prepared as described in Example 10a, of Bender et al., U.S. Aplication Serial Number 07/365,349, filed June 13, 1989, whose disclosure is incorporated by reference herein, is dissolved in 20 ml of dry methylene chloride containing 5.29 g (66.9 mmoles) of pyridine was treated with 3.63 g (33.4 mmoles) of ethyl chloroformate over one hour. After 72 hours, the mixture was poured into 0.3 N HCl at 0°C and extracted into methylene chloride. The organic phase was washed with 0.3 N HCl, water and then dried over anhydrous sodium sulfate. The solvent was stripped in vacuo to give the title compound as a tan powder; ^{1}H-NMR (250 MHz, $CDCl_3$) o 8.17 (d,1 H), 7.60 (d,1 H), 7.50 (d,2 H), 7.12 (d-d,1 H), 7.0 (br s,2 H), 6.92 (d,2 H), 6.76 (t,1 H), 5.02 (p,1 H), 4.79 (br s,2 H), 4.32 (q,2 H), 3.76 (s,3 H), 1.30 (t,3 H).

c) 2-(4-Methoxyphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

A mixture of 1.2 g (3.20 mmoles) of 2-(4-methoxy-phenyl)-3-(1-ethoxycarbonyl-1,4-dihydropyridyl)-imidazo[1,2-a]pyridine, prepared as described in Example 10b, of Bender et al., U.S. Aplication Serial Number 07/365,349, filed June 13, 1989, in 10 ml of decalin was heated at 185 to 190°C under argon with 0.154 g (4.8 mmoles) of sublimed sulfur for 1.5 hours. The cooled reaction mixture was extracted with 3N HCl and the aqueous layer washed with methylene chloride, made alkaline with 5% sodium carbonate solution and extracted with methylene chloride. The basic organic phase was dried over anhydrous potassium carbonate and stripped in vacuo. The residue was chromatographed on silica and eluted with 1 to 8% of methanol in chloroform/ethyl acetate (1:1). Recrystallization two times from ethyl acetate/ether and once from ethyl acetate/hexane gave the title compound, mp 127.5-128.5°C, Calcd for $C_{19}H_{15}N_3O$; C: 75.73, H: 5.02, N: 13.94; found C: 75.96, H: 5.05, N: 14.00.

EXAMPLE 18

2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

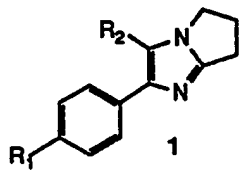
To a stirred solution of 5.0 g (16.3 mmoles) of 2-(4-methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine prepared as described in Example 12, of Bender et al., U.S. Application Serial Number 07/365,349, filed June 13, 1989 dissolved in 75 ml of chloroform, chilled in an ice bath, is added dropwise a solution of 3.30 g (16.3 mmoles) of 85% 3-chloroperbenzoic acid in chloroform. After stirring at 25°C overnight, the reaction mixture is washed with 5% sodium carbonate, dried over anhydrous potassium carbonate, and stripped in vacuo. The residue is flash chromatographed on silica eluting with methanol in methylene chloride: 2-propanol (9:1). The solvent is removed in vacuo and the residue recrystallized from ethyl acetate to give the desired titled compound.

In an alternate procedure to that above, 2-(4-propylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine is prepared. The sulfide product (1.4 g) 2-(4-propylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine is prepared, in an analogous method to that described above, and is dissolved in 25 ml of acetic acid and added to a solution containing 1.35 g of potassium persulfate ($K_2S_2O_8$) in 30 ml of water. The reaction is stirred overnight at room temperature and worked up by diluting with methylene chloride neutralizing with potassium carbonate. The residue is columned on silica gel to afford the product.

Example 19

2-(4-Methylsulfoxyphenyl)-3-bromo-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole

A 375 mg (1.21 mmol) portion of [formula 1, R_1 = methylthio, R_2 = bromo] 2-(4-Methylthiophenyl)-3-bromo-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole was dissolved in 4 mL of glacial acetic acid. A 347 mg (1.45 mmol) portion of sodium persulfate was dissolved in 2 mL of water. The two solutions were combined, and the resulting mixture was stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ solution was added, followed by sufficient solid $NaHCO_3$ to make the mixture basic. The mixture was then extracted with three portions of EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and the filtrate was evaporated in vacuo to give 372 mg of white crystalline solid. This material was recrystallized from EtOAc to give 265 mg (67% yield) of 2-(4-Methylsulfinylphenyl)-3-bromo-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole [formula 1 (R_1 = methylsulfoxy, R_2 = bromo] as white blades, mp 181-2°C. FT-IR (KBr, cm^{-1}): 3100-2800 (C-H), 1630 (C=N + C=C), 1085 + 1049 (S=O), 846 (C-H). ^1H NMR ($CDCl_3$): 8.13 (2H, d, J = 8.43), 7.67 (2H, dd, J = 6.82, 1.4), 4.01 (2H, t, J = 7.12), 3.02 (2H, t, J = 7.6), 2.75 (3H, s), 2.66 (2H, quint, J = 7.35). ^{13}C NMR ($CDCl_3$): 154.32, 143.63, 140.50, 136.61, 126.79, 123.65, 95.37, 44.76, 43.95, 25.25, 24.30. CI-MS (NH_3): 328 (15), 327 (89), 326 (19), 325, ($(M + H)^+$, 100), 311 (40), 309 (41), 247 (34), 231 (20). Elemental analysis: Calc'd for $C_{13}H_{13}BrNO_2S$, C 48.01, H 4.03, N, 8.61; found, C 48.16, H, 4.03, N 8.77.



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EXAMPLE 20

2-(4-Methylsulfoxyphenyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole

A 32 mg (0.139 mmol) portion of 2-(4-Methylthiophenyl)-6,7-dihydro-[5H]pyrrolo[1,2-a]imidazole (formula 1, R_1 = methylthio, R_2 = H), was dissolved in 0.5 mL of glacial acetic acid, and combined with a solution of 40 mg (0.167 mmol) of sodium persulfate in 0.3 mL water. The resulting mixture was stirred at room temperature for 3 h, then worked up as in Example 1, giving 39 mg of product as a brown oil. This was separated on a preparative TLC plate developed twice in 1:9 (v/v) ethanol:methylene chloride to give 12.5 mg (36% yield) of 1 (R_1 = methylsulfinyl, R_2 = H) as a clear glass. FT-IR (film): 3100-2800 (C-H), 1598 + 1545 (C=C), 1385 (C-N or C-H), 1088 + 1043 (S=O) 953 (=C-H), 840 (C-H), 752 (C-S). ^1H NMR ($CDCl_3$): 7.89 (2H, d, J = 8.5), 7.63 (2H, d, J = 8.5), 7.27 (1H, s), 4.04 (2H, t, J = 7.1), 2.95 (2H, t, 7.5), 2.74 (3H, s), 2.64 (2H, quint, J = 7.3). ^{13}C NMR ($CDCl_3$): 155.41, 144.97, 142.92, 137.86, 125.27, 123.98, 111.52, 44.93, 43.91, 26.09, 21.14. DCI-MS (CH_4): 249 (12), 248

(15), 247 ((M + H)$^+$, 100), 231 (4), 230 (4), 184 (2). HRMS (CI- CH_4): required for $C_{13}H_{14}N_2OS$, 247.0913 for (M + H); found, 247.0909.

EXAMPLE 21

2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole

To a solution of 154 mg (0.5 mmol) of 2-(4-Methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole in 2 mL of glacial acetic acid was added dropwise an aqueous solution of potassium persulfate (135 mg, 0.5 mmol in 3.5 mL) at room temperature. The reaction mixture was stirred for 22 h, producing a clear yellow solution. The pH of the solution was adjusted to 8-9 by the addition of solid potassium carbonate, and then extracted four times with 20 mL of methylene chloride. The combined extracts were washed successively with 25 mL water, 25 mL of saturated aqueous sodium chloride solution, then dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was evaporated in vacuo. The resulting oil solidified on standing at room temperature, then was slurried in ethyl acetate and the solvent filtered off, giving 108 mg (67% yield) of 2-(4-Methylsulfoxyphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole. TLC analysis (Analtech SiO_2, 95:5 methylene chloride:methanol) showed the absence of any sulfone derivative, and the presence of a single spot comigrating with the methylsulfoxy derivative.

EXAMPLE 22

2-(4-Methylsulfoxyphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole

To a solution of 154 mg (0.5 mmol) of 2-(4-Methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole in 2 mL of glacial acetic acid was added dropwise an aqueous solution of sodium persulfate (143 mg, 0.6 mmol in 1 mL) at room temperature. The reaction mixture was stirred for 28 h. A 50 mL portion of water added, the pH was adjusted to 8-9 by the addition of solid potassium carbonate, and then the mixture was extracted three times with 20 mL of methylene chloride. The combined extracts were washed successively with 25 mL water, 25 mL of saturated aqueous sodium chloride solution, then dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was evaporated in vacuo. After drying for 18 h at 56°C/35 mm of Hg, the solid weighed 153.6 mg for a chemical yield of 95%. The chemical purity was determined by HPLC to be 92%. No sulfone derivative was detected by HPLC.

EXAMPLE 23

2-(4-propylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]pyrrolo[1,2-a]imidazole

The sulfide (1.4 g) 2-(4-propylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo [1,2-a] imidazole was prepared as described in Example 3 of US Patent No.

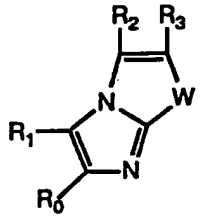
Adams et al., U.S. Patent 4,719,218, issued 01/12/88, and see Example 18 of this application as well, and was dissolved in 25 ml of acetic acid and added to a solution containing 1.35 g of potassium persulfate ($K_2S_2O_8$) in 30 ml of water. The reaction was stirred overnight at room temperature and worked up by diluting with methylene chloride neutralizing with potassium carbonate. The residue was columned on silica gel to afford the product and then further purified by recrystalization from ether/methylene chloride: m.p. 114-116°C; mass spec (DCI/NH_3) 352(M+1), 336. Analysis Calcd. for $C_{20}H_{21}N_3SO$: C, 68.35; H, 6.02; N, 11.96; S, 9.12. Found: C, 68.17; H, 6.14; N, 11.97; S, 9.05.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

CLAIMS

What is claimed is:

1. A method of treating an OPUFA mediated disease in a subject in need thereof which comprises administering to such subject an effective OPUFA inhibiting amount of a compound of the formula:



FORMULA (I)

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3}alkanamido), N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy or 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl alkylthioalkylthio, Z, or acyloxyalkylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4}alkyl, C_{1-3} alkylamino, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido, C_{1-3} dialkylamino, amino, N-pyrrolidino or N-piperidino;

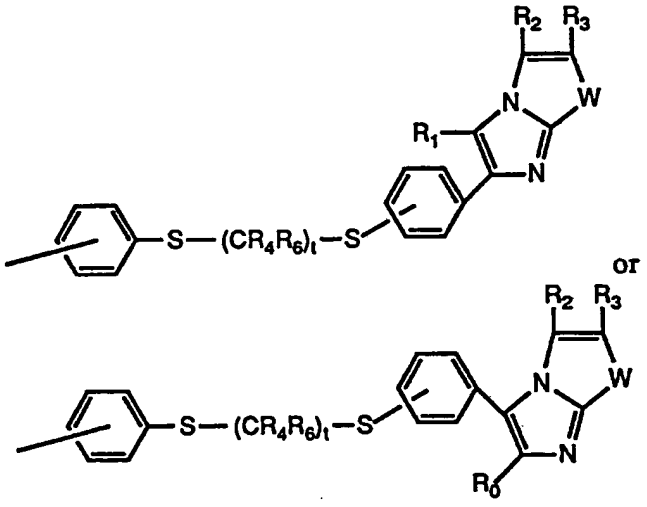
(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, CF_3, C_{1-4} alkyl, and the other substituent is thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio,

alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(d) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(e) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, or hydroxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkyl-sulfonyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} -1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio, Z, or acyloxyalkylthio; or wherein the substituents together form a methylene dioxy group;

(f) a moiety of one of the following formulae:



wherein t is 0 or 1;

R_4 and R_6 are independently selected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;

Z is $-S-(CR_4R_6)_t-S-Z_1$;

Z_1 is C_{1-9} alkyl, aryl or heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. The method according to Claim 1 wherein

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is halo, C_{1-3} alkylamino, C_{1-3} dialkylamino, thiol, hydroxy, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, acyloxyalkylthio, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, acylthio, 1-acyloxy-1-alkylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio; or

(e) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkoxy, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group.

3. The method of Claim 2 wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S-, or -O-;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-posidon of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, acyloxyalkylthio, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, C_{1-3} alkylamino, or C_{1-3} dialkylamino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, acylthio, 1-acyloxy-1-alkylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio; or

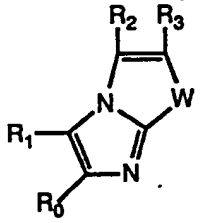
(e) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkoxy, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group.

4. The method according to Claim 2 which is 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine.

5. The method according to Claim 1 to 4 wherein the enzyme 5-lipoxygenase is inhibited.

6. The method of treatment according to Claim 5 wherein the OPUFA mediated disease is selected from arthritis, rheumatoid arthritis, osteoarthritis, allergic rhinitis, psoriasis, dermatitis, ischemic induced myocardial injury, reperfusion injury, gout, asthma, adult respiratory distress syndrome, atherosclerosis, inflammatory bowel disease, stroke, spinal cord injury or traumatic brain injury.

7. A method of treating a cyclooxygenase pathway mediated disease in a subject in need thereof which comprises administering to such subject an effective, non-toxic cyclooxygenase pathway inhibiting amount of a compound of the formula:



FORMULA (I)

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-}

5 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3}alkanamido), N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy or 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl alkylthioalkylthio, Z, or acyloxyalkylthio;

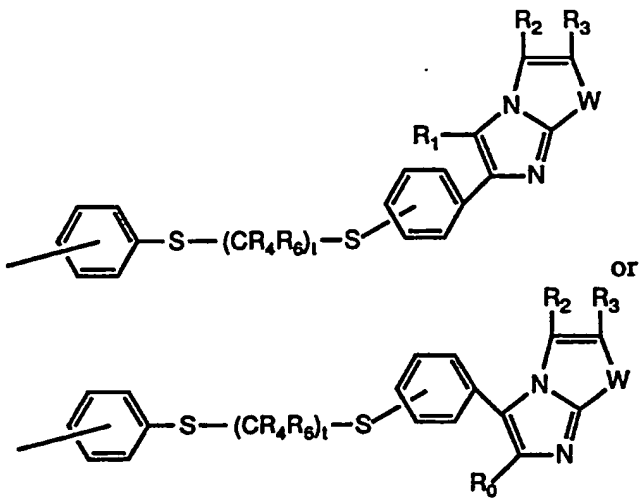
(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, C_{1-3} alkylamino, N-(C_{1-3}alkyl)-N-(C_{1-3} alkanamido, C_{1-3} dialkylamino, amino, N-pyrrolidino or N-piperidino;

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, CF_3, C_{1-4} alkyl, and the other substituent is thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(d) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxy-alkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(e) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, or hydroxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkyl-sulfonyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} -1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio, Z, or acyloxyalkylthio; or wherein the substituents together form a methylene dioxy group;

(f) a moiety of one of the following formulae:



wherein t is 0 or 1;

R_4 and R_6 are independently selected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;

Z is $-S-(CR_4R_6)_t-S-Z_1$;

Z_1 is C_{1-9} alkyl, aryl or heteroaryl;

or a pharmaceutically acceptable salt thereof.

8. The method according to Claim 7 wherein the other of R_1 and R_0 is

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is halo, CF_3, C_{1-3} alkylamino, C_{1-3} dialkylamino, thiol, hydroxy, C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, acyloxyalkylthio, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, acylthio, 1-acyloxy-1-alkylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio; or

(e) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkoxy, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group.

9. The method of Claim 8 wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$;

R_2 and R_3 are hydrogen,

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, acyloxyalkylthio, or acylthio;

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, C_{1-3} alkylamino, or C_{1-3} dialkylamino; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, acylthio, 1-acyloxy-1-alkylthio and the other is C_{1-3} alkoxy or halo; or

(d) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylamino, C_{1-3} dialkylamino and the other is selected from acylthio, alkylsulfinyl, phenylsulfinyl or acyloxyalkylthio; or

(e) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkoxy, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group.

10. The method according to Claim 9 which is 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine.

11. The method according to Claim 7 wherein the cyclooxygenase disease state is pyresis, pain, osteoarthritis, rheumatoid arthritis, thrombosis, inflammation, uticaria or edema.

12. A method of treating an OPUFA mediated disease in a subject in need thereof which comprises administering to such subject an effective, OPUFA inhibiting amount of

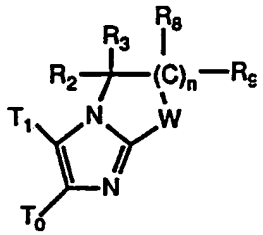
2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]-imidazole; 5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or 5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole or a pharmaceutically acceptable salt thereof.

13. The method according to Claim 12 wherein the OPUFA mediated disease is selected from arthritis, rheumatoid arthritis, osteoarthritis, allergic rhinitis, psoriasis, dermatitis, ischemic induced myocardial injury, reperfusion injury, gout, asthma, adult respiratory distress syndrome, atherosclerosis, inflammatory bowel disease, stroke, spinal cord injury or traumatic brain injury.

14. The method according to Claim 13 wherein the enzyme 5-lipoxygenase is inhibited.

15. A method of treating a cycloxygenase pathway mediated disease in a subject in need thereof which comprises administering to such subject an effective cyclooxygenase inhibiting amount of
2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]-imidazole; 5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or 5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole; or a pharmaceutically acceptable salt thereof.

16. A compound of the formula



Formula (II)

wherein

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;

and one of T_1 and T_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when T_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of T_1 and T_0 is

(a) monosubstituted phenyl wherein said substituent is hydroxy, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{3-5} 2-

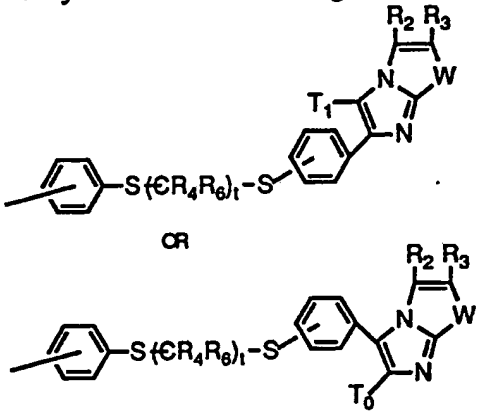
alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-C_{1-3} -alkanamido, N-(C_{1-3} alkyl)-N-(C_{1-3} alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio , or Z; or

(b) disubstituted phenyl wherein one of said substituents is amino, N-C_{1-3} -alkanamido, N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, or N-piperidino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(c) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, hydroxy, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio, or Z; or

(d) disubstituted phenyl wherein said substituents are, independently C_{1-3} alkylamino, C_{1-3} dialkylamino, amino, N-(C_{1-3}alkyl)-N-(C_{1-3} alkanamido, N-pyrrolidino or N-piperidino; or

(e) a moiety of one of the following formulae:



wherein t is 0 or 1;

R_4 and R_6 are independently selected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;

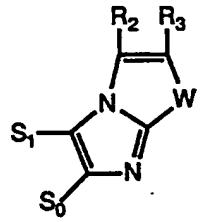
Z is -S-(CR_4R_6)$_t$-S-Z_1;
Z_1 is C_{1-9} alkyl, aryl or heteroaryl;
or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition according comprising a compound of Claim 16 and a pharmaceutically acceptable carrier or diluent.

18. A method of treating an OPUFA mediated disease, in a mammal in need thereof, which process comprises administering to said mammal an effective OPUFA inhibiting amount of a compound according to Claim 16..

19. The method according to Claim 18 wherein the enzyme 5-lipoxygenase is inhibited.

20. A pharmaceutical composition for use in medicine for treatment of an OPUFA or cyclooxygenase mediated disease state comprising a pharmaceutically acceptable carrier or diluent and a compound of Formula (III):



Formula (III)

wherein W is -CR_5=CR_7-, -N=CR_7-, -S- or -O-;
R_2, R_3, R_5, and R_7 are, independently, -H or C_{1-2} alkyl;
and one of S_1 and S_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when S_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of S_1 and S_0 is

(a) monosubstituted phenyl wherein said substituent is -H, C_{1-4} alkyl, halo, C_{1-2} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, or acyloxyalkylthio; or

(b) disubstituted phenyl wherein said substitutents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, or C_{1-4} alkyl; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl; and the other is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, or acyloxyalkylthio: or

(d) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkylsulinfyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} -1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, or acyloxyalkylthio; or wherein the substituents together form a methylene dioxy;

and the pharmaceutically acceptable salts thereof.

21. A pharmaceutical composition for use in treating an OPUFA mediated disease comprising a pharmaceutically acceptable carrier or diluent and a compound selected from

2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]-imidazole;

5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or

5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole; or pharmaceutically acceptable salt thereof.

22. A process for oxidizing arylsulfides to arylsulfoxides wherein the aryl sulfide is a substituent group on a heteroaromatic nitrogen containing ring system, which process comprises treating said arylsulfide with sodium or potassium persulfate in aqeuous acetic acid to yield the corresponding aryl sulfoxide derivative; provided that the heteroaromatic ring is other than a 2-(C_{1-3} alkylsulfidephenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[2,1-a]imidazole ring system when the oxidant is potassium persulfate.

23. The process according to Claim 22 wherein the aryl sulfide is a phenylsulfide moiety.

24. The process according to Claim 23 wherein the aryl sulfide is an alkyl or aryl substituted sulfide.

25. The process according to Claim 24 wherein the alkyl substituted sulfide is methylthio or ethylthio.

26. The process according to Claim 25 wherein the oxidant is potassium persulfate.

27. The process according to Claim 26 wherein the oxidant is sodium persulfate.

28. The process according to Claim 26 or 27 wherein the reaction temperature is from about 0° C to about 60° C.

29. The process according to Claim 22 wherein an additional co-solvent, such as acetone or THF is used.

30. The process according to Claim 22 wherein the heteroaromatic nitrogen containing ring system is selected from pyrrole, pyrazole, imidazole, imidazolididine, pyrazolidine, pyrazoline, morpholine, pyridine, pyrazine, indolizine, indoline, purine, quinoline, isoquinoline, napthyridine, triazole, pyrimidine, piperidine, isoindole, 3H-indole, cinnoline, carbazole, phenanthradine, phenazine, isothiazole, imidazo[1,2-b]-[1,2,4]triazine, triazine, pyridazine, 6,7-dihydro-[5H]-pyrrolo[2,1-a]imidazole, 2,3-dihydroimidazo[2,1-b]-thiazole, imidazo[2,1-b]thiazole, 2,3,4,5 tetrahydro-imidazo-[2,1-b]thiazole, imidazo[2,1-b]oxazole, imidazo[1,2-a]pyridine; 5,6,7,8-tetrahydroimidazo-[1,2-a]pyridine, or a imidazo[1,2-a]pyrimidine ring system.

31. The process according to Claim 22 wherein the oxidant is sodium persulfate and the heteroaromatic nitrogen containing ring is 3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[2,1-a]imidazole ring and the aryl sulide is 2-methylthiophenyl or 2-propylthiophenyl.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04022

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5) A61K/ 31/44

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S. CL.	514-279

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

Cas on line - U.S. file

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Chemical abstracts Vol. 108-37829B (1988). Kokai Tokkyokoho JP Entire Article	1-21

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

22 October 1991

Date of Mailing of this International Search Report

13 NOV 1991

International Searching Authority

ISA/US

Signature of Authorized Officer

S. Friedman

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [2] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . . . , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

I. Claims 1-21 - compositions and methods of use.
II. Claims 22-31 - Process for preparation Group I is the first mentioned inventive concept and was examined PCT Article 17 (3) (a)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

I. Claims 1-21 - compositions and methods of use.

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.